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(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertääke (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ERIKSSON, Anders** [SE/SE]; AstraZeneca R & D, S-221 87 Lund (SE). **LEPISTÖ, Matti** [SE/SE]; AstraZeneca R & D Lund, S-221 87 Lund (SE). **LUNDKVIST, Michael** [SE/SE]; AstraZeneca R & D, S-221 87 Lund (SE). **MUNCK AF ROSENSCHÖLD, Magnus** [SE/SE]; AstraZeneca R & D, S-221 87 Lund (SE). **ZLATOIDSKY, Pavol** [SK/SE]; AstraZeneca R & D, S-221 87 Lund (SE).

(74) Agent: **GLOBAL INTELLECTUAL PROPERTY ASTRAZENCA AB**; AstraZeneca AB, S-151 85 Södertälje (SE).

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(54) Title: METALLOPROTEINASE INHIBITORS

(57) Abstract: The invention provides a metalloproteinsae inhibitor compound comprising a metal binding group having formula (I), for use in the treatment of a disease or condition mediated by one or more metalloproteinase enzymes wherein X is selected from NR1, O, S; B is C or CH, Y1 and Y2 are idenpendently selected from O, S; R1 is selected from H, alkyl, haloalkyl.

METALLOPROTEINASE INHIBITORS

The present invention relates to the use of compounds for inhibiting metalloproteinases and in particular to the use of pharmaceutical compositions as therapeutic agents.

The compounds for use according to this invention are inhibitors of one or more metalloproteinase enzymes. Metalloproteinases are a superfamily of proteinases (enzymes) whose numbers in recent years have increased dramatically. Based on structural and functional considerations these enzymes have been classified into families and subfamilies as described in N.M. Hooper (1994) FEBS Letters 354:1-6. Examples of metalloproteinases include the matrix metalloproteinases (MMPs) such as the collagenases (MMP1, MMP8, MMP13), the gelatinases (MMP2, MMP9), the stromelysins (MMP3, MMP10, MMP11), matrilysin (MMP7), metalloelastase (MMP12), enamelysin (MMP19), the MT-MMPs (MMP14, MMP15, MMP16, MMP17); the reprolysin or adamalysin or MDC family which includes the secretases and sheddases such as TNF converting enzymes (ADAM10 and TACE); the astacin family which include enzymes such as procollagen processing proteinase (PCP); and other metalloproteinases such as aggrecanase, the endothelin converting enzyme family and the angiotensin converting enzyme family.

Metalloproteinases are believed to be important in a plethora of physiological disease processes that involve tissue remodelling such as embryonic development, bone formation and uterine remodelling during menstruation. This is based on the ability of the metalloproteinases to cleave a broad range of matrix substrates such as collagen, proteoglycan and fibronectin. Metalloproteinases are also believed to be important in the processing, or secretion, of biological important cell mediators, such as tumour necrosis factor (TNF); and the post translational proteolysis processing, or shedding, of biologically important membrane proteins, such as the low affinity IgE receptor CD23 (for a more complete list see N. M. Hooper *et al.*, (1997) Biochem J. 321:265-279).

Metalloproteinases have been associated with many diseases or conditions. Inhibition of the activity of one or more metalloproteinases may well be of benefit in these diseases or conditions, for example: various inflammatory and allergic diseases such as, inflammation of the joint (especially rheumatoid arthritis, osteoarthritis and gout), inflammation of the gastro-intestinal tract (especially inflammatory bowel disease, ulcerative colitis and gastritis), inflammation of the skin (especially psoriasis, eczema, dermatitis); in tumour metastasis or invasion; in disease associated with uncontrolled degradation of the extracellular matrix such as osteoarthritis; in bone resorptive disease (such as osteoporosis and Paget's disease); in diseases associated with aberrant angiogenesis; the enhanced collagen remodelling associated with diabetes, periodontal disease (such as gingivitis), corneal ulceration, ulceration of the skin, post-operative conditions (such as colonic anastomosis) and dermal wound healing; demyelinating diseases of the central and peripheral nervous systems (such as multiple sclerosis); Alzheimer's disease; extracellular matrix remodelling observed in cardiovascular diseases such as restenosis and atherosclerosis; asthma; rhinitis; and chronic obstructive pulmonary diseases (COPD).

MMP12, also known as macrophage elastase or metalloelastase, was initially cloned in the mouse by Shapiro *et al* [1992, Journal of Biological Chemistry 267: 4664] and in man by the same group in 1995. MMP-12 is preferentially expressed in activated macrophages, and has been shown to be secreted from alveolar macrophages from smokers [Shapiro *et al*, 1993, Journal of Biological Chemistry, 268: 23824] as well as in foam cells in atherosclerotic lesions [Matsumoto *et al*, 1998, Am J Pathol 153: 109]. A mouse model of COPD is based on challenge of mice with cigarette smoke for six months, two cigarettes a day six days a week. Wildtype mice developed pulmonary emphysema after this treatment. When MMP12 knock-out mice were tested in this model they developed no significant emphysema, strongly indicating that MMP-12 is a key enzyme in the COPD pathogenesis. The role of MMPs such as MMP12 in COPD (emphysema and bronchitis) is discussed in Anderson and Shinagawa, 1999, Current Opinion in Anti-inflammatory and Immunomodulatory Investigational Drugs 1(1): 29-38. It was recently discovered that

smoking increases macrophage infiltration and macrophage-derived MMP-12 expression in human carotid artery plaques Kangavari [Matetzky S, Fishbein MC *et al.*, Circulation 102:(18), 36-39 Suppl. S, Oct 31, 2000].

MMP13, or collagenase 3, was initially cloned from a cDNA library derived from a breast tumour [J. M. P. Freije *et al.* (1994) Journal of Biological Chemistry 269(24):16766-16773]. PCR-RNA analysis of RNAs from a wide range of tissues indicated that MMP13 expression was limited to breast carcinomas as it was not found in breast fibroadenomas, normal or resting mammary gland, placenta, liver, ovary, uterus, prostate or parotid gland or in breast cancer cell lines (T47-D, MCF-7 and ZR75-1). Subsequent to this observation MMP13 has been detected in transformed epidermal keratinocytes [N. Johansson *et al.*, (1997) Cell Growth Differ. 8(2):243-250], squamous cell carcinomas [N. Johansson *et al.*, (1997) Am. J. Pathol. 151(2):499-508] and epidermal tumours [K. Airola *et al.*, (1997) J. Invest. Dermatol. 109(2):225-231]. These results are suggestive that MMP13 is secreted by transformed epithelial cells and may be involved in the extracellular matrix degradation and cell-matrix interaction associated with metastasis especially as observed in invasive breast cancer lesions and in malignant epithelia growth in skin carcinogenesis.

Recent published data implies that MMP13 plays a role in the turnover of other connective tissues. For instance, consistent with MMP13's substrate specificity and preference for degrading type II collagen [P. G. Mitchell *et al.*, (1996) J. Clin. Invest. 97(3):761-768; V. Knauper *et al.*, (1996) The Biochemical Journal 271:1544-1550], MMP13 has been hypothesised to serve a role during primary ossification and skeletal remodelling [M. Stahle-Backdahl *et al.*, (1997) Lab. Invest. 76(5):717-728; N. Johansson *et al.*, (1997) Dev. Dyn. 208(3):387-397], in destructive joint diseases such as rheumatoid and osteo-arthritis [D. Wernicke *et al.*, (1996) J. Rheumatol. 23:590-595; P. G. Mitchell *et al.*, (1996) J. Clin. Invest. 97(3):761-768; O. Lindy *et al.*, (1997) Arthritis Rheum 40(8):1391-1399]; and during the aseptic loosening of hip replacements [S. Imai *et al.*, (1998) J. Bone Joint Surg. Br. 80(4):701-710]. MMP13 has also been implicated in chronic adult periodontitis as it has been localised to the epithelium of chronically inflamed mucosa human gingival tissue [V. J. Uitto *et al.*, (1998) Am. J. Pathol

152(6):1489-1499] and in remodelling of the collagenous matrix in chronic wounds [M. Vaalamo *et al.*, (1997) J. Invest. Dermatol. 109(1):96-101].

MMP9 (Gelatinase B; 92kDa TypeIV Collagenase; 92kDa Gelatinase) is a secreted protein which was first purified, then cloned and sequenced, in 1989 [S.M. Wilhelm *et al* (1989) J. Biol Chem. 264 (29): 17213-17221; published erratum in J. Biol Chem. (1990) 265 (36): 22570]. A recent review of MMP9 provides an excellent source for detailed information and references on this protease: T.H. Vu & Z. Werb (1998) (In : Matrix Metalloproteinases. 1998. Edited by W.C. Parks & R.P. Mecham. pp115 - 148. Academic Press. ISBN 0-12-545090-7). The following points are drawn from that review by T.H. Vu & Z. Werb (1998).

The expression of MMP9 is restricted normally to a few cell types, including trophoblasts, osteoclasts, neutrophils and macrophages. However, it's expression can be induced in these same cells and in other cell types by several mediators, including exposure of the cells to growth factors or cytokines. These are the same mediators often implicated in initiating an inflammatory response. As with other secreted MMPs, MMP9 is released as an inactive Pro-enzyme which is subsequently cleaved to form the enzymatically active enzyme. The proteases required for this activation *in vivo* are not known. The balance of active MMP9 versus inactive enzyme is further regulated *in vivo* by interaction with TIMP-1 (Tissue Inhibitor of Metalloproteinases -1), a naturally-occurring protein. TIMP-1 binds to the C-terminal region of MMP9, leading to inhibition of the catalytic domain of MMP9. The balance of induced expression of ProMMP9, cleavage of Pro- to active MMP9 and the presence of TIMP-1 combine to determine the amount of catalytically active MMP9 which is present at a local site. Proteolytically active MMP9 attacks substrates which include gelatin, elastin, and native Type IV and Type V collagens; it has no activity against native Type I collagen, proteoglycans or laminins.

There has been a growing body of data implicating roles for MMP9 in various physiological and pathological processes. Physiological roles include the invasion of embryonic trophoblasts through the uterine epithelium in the early stages of embryonic

implantation; some role in the growth and development of bones; and migration of inflammatory cells from the vasculature into tissues.

MMP-9 release, measured using enzyme immunoassay, was significantly enhanced in fluids and in AM supernantants from untreated asthmatics compared with those from other populations [Am. J. Resp. Cell & Mol. Biol., Nov 1997, 17 (5):583-591]. Also, increased MMP9 expression has been observed in certain other pathological conditions, thereby implicating MMP9 in disease processes such as COPD, arthritis, tumour metastasis, Alzheimer's, Multiple Sclerosis, and plaque rupture in atherosclerosis leading to acute coronary conditions such as Myocardial Infarction.

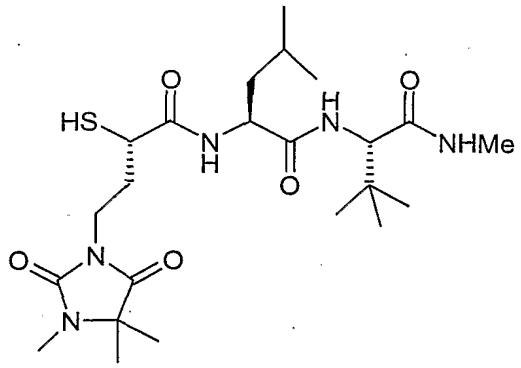
MMP-8 (collagenase-2, neutrophil collagenase) is a 53 kD enzyme of the matrix metalloproteinase family that is preferentially expressed in neutrophils. Later studies indicate MMP-8 is expressed also in other cells, such as osteoarthritic chondrocytes [Shlopov *et al*, 1997, Arthritis Rheum, 40:2065]. MMPs produced by neutrophils can cause tissue remodelling, and hence blocking MMP-8 should have a positive effect in fibrotic diseases of for instance the lung, and in degradative diseases like pulmonary emphysema. MMP-8 was also found to be up-regulated in osteoarthritis, indicating that blocking MMP-8 many also be beneficial in this disease.

MMP-3 (stromelysin-1) is a 53 kD enzyme of the matrix metalloproteinase enzyme family. MMP-3 activity has been demonstrated in fibroblasts isolated from inflamed gingiva [Uitto V. J. *et al*, 1981, J. Periodontal Res., 16:417-424], and enzyme levels have been correlated to the severity of gum disease [Overall C. M. *et al*, 1987, J. Periodontal Res., 22:81-88]. MMP-3 is also produced by basal keratinocytes in a variety of chronic ulcers [Saarialho-Kere U. K. *et al*, 1994, J. Clin. Invest., 94:79-88]. MMP-3 mRNA and protein were detected in basal keratinocytes adjacent to but distal from the wound edge in what probably represents the sites of proliferating epidermis. MMP-3 may thus prevent the epidermis from healing. Several investigators have demonstrated consistent elevation of MMP-3 in synovial fluids from rheumatoid and osteoarthritis patients as compared to controls [Walakovits L. A. *et al*, 1992, Arthritis Rheum., 35:35-42; Zafarullah M. *et al*, 1993, J. Rheumatol., 20:693-697]. These studies provided the basis for the belief that an

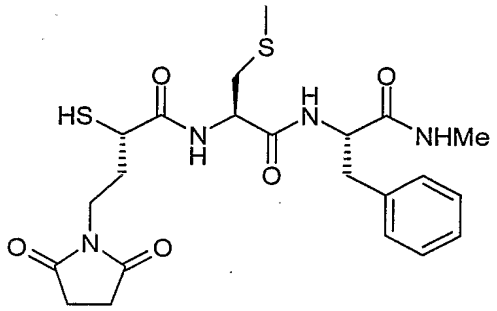
inhibitor of MMP-3 will treat diseases involving disruption of extracellular matrix resulting in inflammation due to lymphocytic infiltration, or loss of structural integrity necessary for organ function.

A number of metalloproteinase inhibitors are known (see for example the review of MMP inhibitors by Beckett R.P. and Whittaker M., 1998, Exp. Opin. Ther. Patents, 8(3):259-282]. Different classes of compounds may have different degrees of potency and selectivity for inhibiting various metalloproteinases.

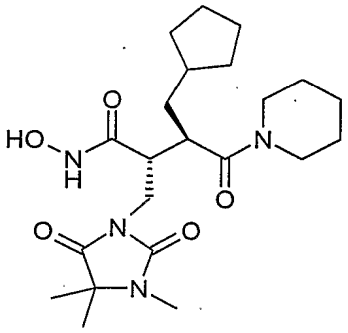
Whittaker M. *et al* (1999, Chemical Reviews 99(9):2735-2776] review a wide range of known MMP inhibitor compounds. They state that an effective MMP inhibitor requires a zinc binding group or ZBG (functional group capable of chelating the active site zinc(II) ion), at least one functional group which provides a hydrogen bond interaction with the enzyme backbone, and one or more side chains which undergo effective van der Waals interactions with the enzyme subsites. Zinc binding groups in known MMP inhibitors include carboxylic acid groups, hydroxamic acid groups, sulfhydryl or mercapto, etc. For example, Whittaker M. *et al* discuss the following MMP inhibitors:



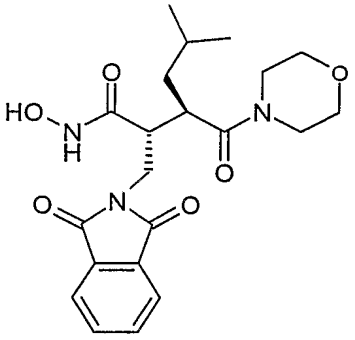
The above compound entered clinical development. It has a mercaptoacyl zinc binding group, a trimethylhydantoinylethyl group at the P1 position and a leucinyl-*tert*-butyllglycinyl backbone.



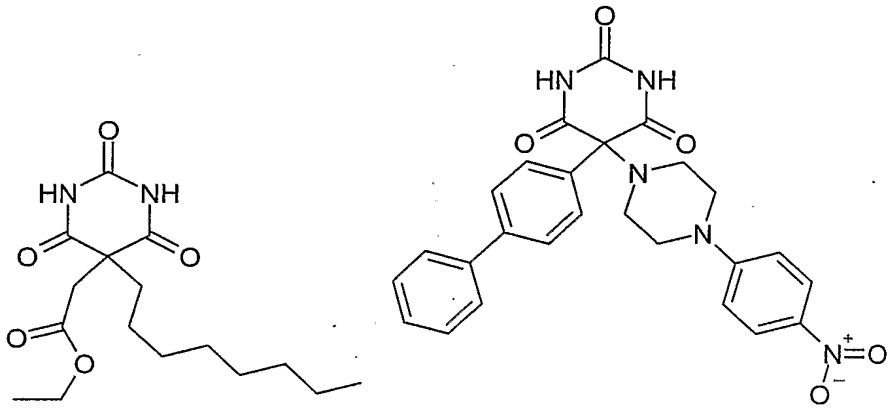
The above compound has a mercaptoacyl zinc binding group and an imide group at the P1 position.



The above compound was developed for the treatment of arthritis. It has a non-peptidic succinyl hydroxamate zinc binding group and a trimethylhydantoinylethyl group at the P1 position.



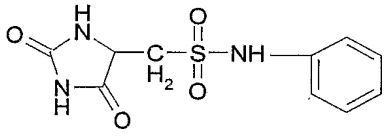
The above compound is a phthalimido derivative that inhibits collagenases. It has a non-peptidic succinyl hydroxamate zinc binding group and a cyclic imide group at P1. Whittaker M. *et al* also discuss other MMP inhibitors having a P1 cyclic imido group and various zinc binding groups (succinyl hydroxamate, carboxylic acid, thiol group, phosphorous-based group).

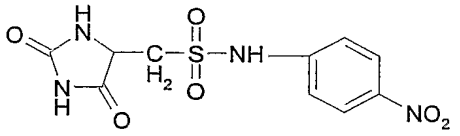


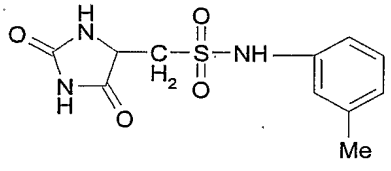
The above compounds appear to be good inhibitors of MMP8 and MMP9 (PCT patent applications WO9858925, WO9858915). They have a pyrimidin-2,3,4-trione zinc binding group.

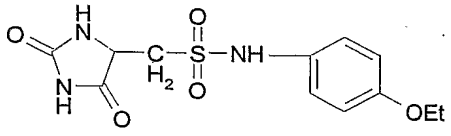
The following compounds are not known as MMP inhibitors:-

Lora-Tamayo, M *et al* (1968, An. Quim 64(6): 591-606) describe synthesis of the following compounds as a potential anti-cancer agent:

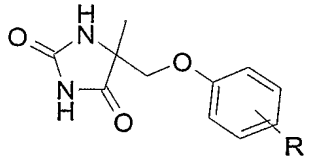


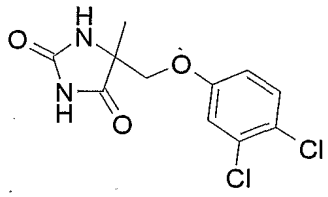






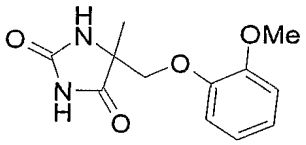
Czech patent numbers 151744 (19731119) and 152617 (1974022) describe the synthesis and the anticonvulsive activity of the following compounds:

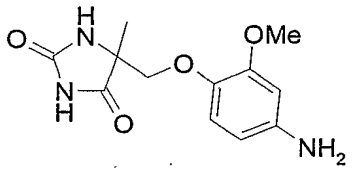


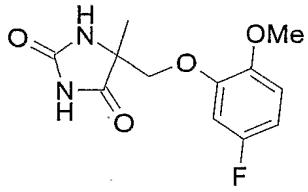


R= 4-NO2, 4-OMe, 2-NO2,

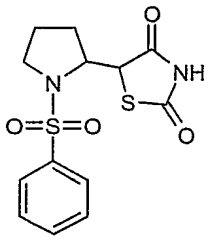
US patent number 3529019 (19700915) describes the following compounds used as intermediates:

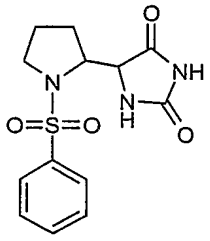




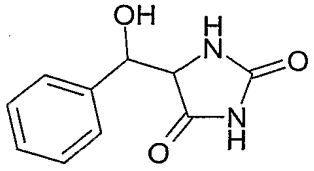


PCT patent application number WO 00/09103 describes compounds useful for treating a vision disorder, including the following (compounds 81 and 83, Table A, page 47):

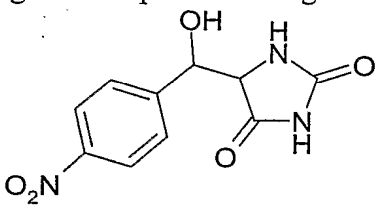




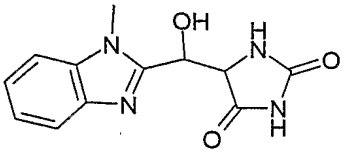
Japanese patent number 5097814 (1993) describes a method of preparing compounds useful as intermediates for production of antibiotics, including the compound having the formula:



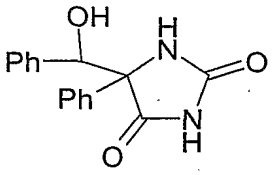
Morton *et al* (1993, J Agric Food Chem 41(1): 148-152) describe preparation of compounds with fungicidal activity, including the compound having the formula:

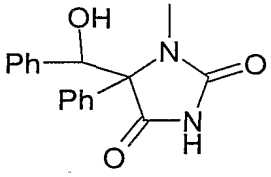


Dalgatov, D *et al* (1967, Khim. Geterotsikl. Soedin. 5:908-909) describe synthesis of the following compound without suggesting a use for the compound:

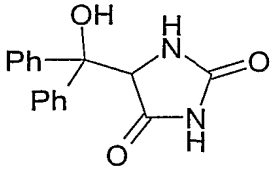


Crooks, P *et al* (1989, J. Heterocyclic Chem. 26(4):1113-17) describe synthesis of the following compounds that were tested for anticonvulsant activity in mice:

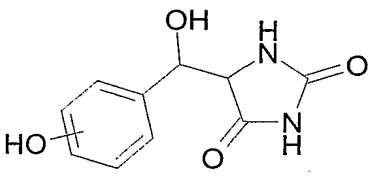


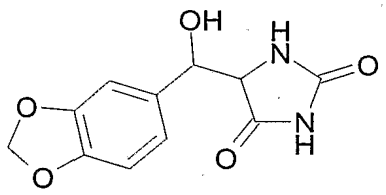


Gramain, J.C *et al* (1990) Recl. Trav. Chim. Pays-Bas 109:325-331) describe synthesis of the following compound:

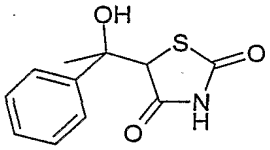


Japanese patent number 63079879 (1988) describes a method for the synthesis of intermediates en route to important amino acids. The following compounds have been used as starting materials:

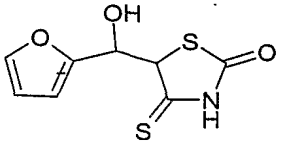


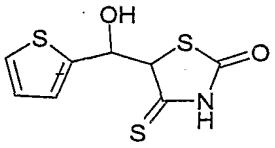


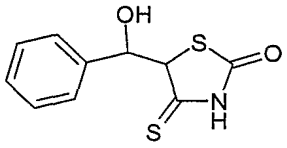
Wolfe, J *et al* (1971, Synthesis 6:310-311) describe synthesis of the following compound without suggesting a use for the compound:



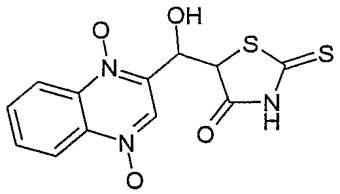
Moharram *et al* (1983, Egypt J. Chem. 26:301-11) describe the following compounds:





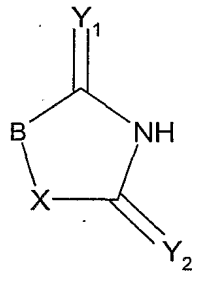


Hungarian patent number 26403 (1983) describes the synthesis and use as food additive of the following compound :



We have now discovered a new class of compounds that act as inhibitors of metalloproteinases and may be used as therapeutic agents, for use in a method of therapeutic treatment of the human or animal body. In particular, we have discovered that such compounds are potent MMP inhibitors and have desirable activity profiles, with beneficial potency, selectivity and/or pharmacokinetic properties. The compounds have a metal binding group that is not found in known metalloproteinase inhibitors.

In a first aspect, the invention provides a metalloproteinase inhibitor compound or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof for use in the treatment of a disease or condition mediated by one or more metalloproteinase enzymes wherein the metalloproteinase inhibitor compound comprises a metal binding group and one or more other functional groups or side chains characterised in that the metal binding group has the formula (I)



(I)

wherein **X** is selected from NR1, O, S;

B is C or CH, and is the point of attachment of the one or more other functional groups or side chains;

Y1 and **Y2** are independently selected from O, S;

R1 is selected from H, alkyl, haloalkyl;

Any alkyl groups outlined above may be straight chain or branched; any alkyl group outlined above is preferably (C1-7)alkyl and most preferably (C1-6)alkyl.

In the metal binding group of formula (I), preferably:

X is NR1;

At least one of Y1 and Y2 is O; especially both Y1 and Y2 are O;

R1 is H, (C1-6)alkyl or halo(C1-6)alkyl; especially R1 is H, (C1-4)alkyl or halo(C1-4)alkyl; most especially R1 is H, (C1-3)alkyl or halo(C1-3)alkyl; particularly R1 is H or alkyl; most particularly R1 is H.

A metalloproteinase inhibitor compound is a compound that inhibits the activity of a metalloproteinase enzyme (for example, an MMP). By way of non-limiting example the inhibitor compound may show IC50s in vitro in the range of 0.1-10000 nanomolar, preferably 0.1-1000 nanomolar.

A metal binding group is a functional group capable of binding the metal ion within the active site of the enzyme. For example, the metal binding group will be a zinc binding group in MMP inhibitors, binding the active site zinc(II) ion. The metal binding group of formula (I) is based on a five-membered ring structure and is preferably a hydantoin group, most preferably a -5 substituted 1-H,3-H-imidazolidine-2,4-dione.

The metal binding group of formula (I) is attached to one or more other functional groups or side chains. Each functional group or side chain may include linear, branched and/or cyclic systems. At least one functional group or side chain (preferably a functional group) should provide a hydrogen bond interaction with the metalloproteinase enzyme backbone, and at least one functional group or side chain (preferably one or more side chains) should undergo effective van der Waals interactions with the enzyme subsites. Suitable groups and/or side chains are chosen such that the resulting compound acts as a metalloproteinase inhibitor.

A metalloproteinase inhibitor compound having a metal binding group of formula (I) or its salt or ester may be used in a method of therapeutic treatment of the human or animal

body. We disclose use in the treatment of a disease or condition mediated by one or more metalloproteinase enzymes. Each of the indications described above for metalloproteinase inhibitors represents an independent and particular embodiment of the invention. In particular we disclose use in the treatment of a disease or condition mediated by one or more MMPs, preferably MMP12 and/or MMP9 and/or MMP13 and/or MMP8 and/or MMP3; especially use in the treatment of a disease or condition mediated by MMP12 or MMP9; most especially use in the treatment of a disease or condition mediated by MMP12.

In a further aspect, the invention provides a method of treating a metalloproteinase mediated disease or condition which comprises administering to a warm-blooded animal a therapeutically effective amount of a metalloproteinase inhibitor compound or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof wherein the metalloproteinase inhibitor compound comprises a metal binding group and one or more other functional groups or side chains characterised in that the metal binding group has the formula (I) as hereinbefore described.

In particular, the metalloproteinase mediated disease or condition is a disease or condition mediated by one or more MMPs, preferably MMP12 and/or MMP9 and/or MMP13 and/or MMP8 and/or MMP3; especially a disease or condition mediated by MMP12 or MMP9; most especially a disease or condition mediated by MMP12.

In a yet further aspect, the invention provides the use of a metalloproteinase inhibitor compound or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof in the preparation of a medicament for use in the treatment of a disease or condition mediated by one or more metalloproteinase enzymes, wherein the metalloproteinase inhibitor compound comprises a metal binding group and one or more other functional groups or side chains characterised in that the metal binding group has the formula (I) as hereinbefore described.

In particular, the disease or condition mediated by one or more metalloproteinase enzymes is a disease or condition mediated by one or more MMPs, preferably MMP12 and/or MMP9 and/or MMP13 and/or MMP8 and/or MMP3; especially a disease or condition mediated by MMP12 or MMP9; most especially a disease or condition mediated by MMP12.

Diseases or conditions mediated by metalloproteinases (metalloproteinase mediated diseases or conditions) include asthma, rhinitis, chronic obstructive pulmonary diseases (COPD), arthritis (such as rheumatoid arthritis and osteoarthritis), atherosclerosis and restenosis, cancer, invasion and metastasis, diseases involving tissue destruction, loosening of hip joint replacements, periodontal disease, fibrotic disease, infarction and heart disease, liver and renal fibrosis, endometriosis, diseases related to the weakening of the extracellular matrix, heart failure, aortic aneurysms, CNS related diseases such as Alzheimer's disease and Multiple Sclerosis (MS), hematological disorders.

The metalloproteinase inhibitor compounds for use according to the invention may be provided as pharmaceutically acceptable salts. These include acid addition salts such as hydrochloride, hydrobromide, citrate and maleate salts and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, or organic amine salt for example triethylamine.

The metalloproteinase inhibitor compounds may also be provided as in vivo hydrolysable esters. These are pharmaceutically acceptable esters that hydrolyse in the human body to produce the parent compound. Such esters can be identified by administering, for example intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluids. Suitable in vivo hydrolysable esters for carboxy include methoxymethyl and for hydroxy include formyl and acetyl, especially acetyl.

In order to use a metalloproteinase inhibitor compound according to the invention or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition for use in the treatment of a disease or condition mediated by one or more metalloproteinase enzymes which comprises a metalloproteinase inhibitor compound or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof and pharmaceutically acceptable carrier, wherein the metalloproteinase inhibitor compound comprises a metal binding group and one or more other functional groups or side chains characterised in that the metal binding group has the formula (I) as hereinbefore described.

The pharmaceutical composition is used in a method of therapeutic treatment of the human or animal body, in the treatment of a disease or condition mediated by one or more metalloproteinase enzymes. Each of the indications described above for metalloproteinase inhibitors represents an independent and particular embodiment of the invention. In particular we disclose use in the treatment of a disease or condition mediated by one or more MMPs, preferably MMP12 and/or MMP9 and/or MMP13 and/or MMP8 and/or MMP3; especially use in the treatment of a disease or condition mediated by MMP12 or MMP9; most especially use in the treatment of a disease or condition mediated by MMP12. Particular disease or conditions include those described above.

The invention further provides a method of treating a metalloproteinase mediated disease or condition which comprises administering to a warm-blooded animal a therapeutically effective amount of a pharmaceutical composition which comprises a metalloproteinase inhibitor compound or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof and pharmaceutically acceptable carrier, wherein the

metalloproteinase inhibitor compound comprises a metal binding group and one or more other functional groups or side chains characterised in that the metal binding group has the formula (I) as hereinbefore described.

In particular, the metalloproteinase mediated disease or condition is a disease or condition mediated by one or more MMPs, preferably MMP12 and/or MMP9 and/or MMP13 and/or MMP8 and/or MMP3; especially a disease or condition mediated by MMP12 or MMP9; most especially a disease or condition mediated by MMP12. Particular diseases or conditions include those described above.

The pharmaceutical compositions may be administered in standard manner for the disease or condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal adminstration or by inhalation. For these purposes the metalloproteinase inhibitor compounds may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions.

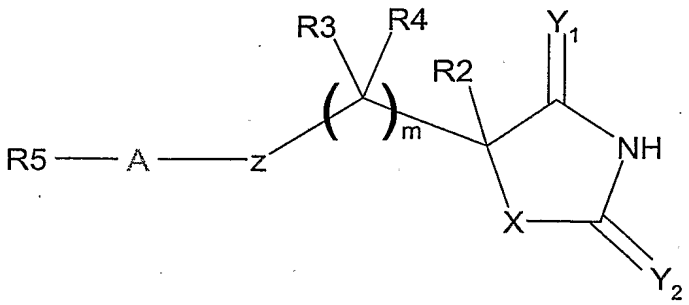
In addition to the metalloproteinase inhibitor compound the pharmaceutical composition may also contain, or be co-administered (simultaneously or sequentially) with, one or more pharmacological agents of value in treating one or more diseases or conditions referred to hereinabove.

The pharmaceutical compositions will normally be administered to humans so that, for example, a daily dose of 0.5 to 75 mg/kg body weight (and preferably of 0.5 to 30 mg/kg body weight) is received. This daily dose may be given in divided doses as necessary, the precise amount of the compound received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease or condition being treated according to principles known in the art.

Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

Metalloproteinase inhibitor compounds for use according to the invention include compounds of the formulae II and III shown below. The metalloproteinase inhibitor compounds of formulae II and III (and salts or esters thereof, and pharmaceutical compositions thereof) are particularly useful in the treatment of a disease or condition mediated by one or more MMP enzymes. They are especially useful in the treatment of a disease or condition mediated by MMP12 and/or MMP9 and/or MMP13 and/or MMP8 and/or MMP3; especially in the treatment of a disease or condition mediated by MMP12 or MMP9; most especially in the treatment of a disease or condition mediated by MMP12. Particular diseases or conditions include those described above.

A compound of formula II



II

wherein

X is selected from NR1, O, S;

Y1 and **Y2** are independently selected from O, S;

Z is selected from O, S, SO, SO_2, $SO_2N(R6)$, $N(R7)SO_2$, $N(R7)SO_2N(R6)$;

m is 1 or 2;

A is selected from a direct bond, (C1-6)alkyl, (C1-6)haloalkyl, or (C1-6)heteroalkyl containing a hetero group selected from N, O, S, SO, SO2 or containing two hetero groups selected from N, O, S, SO, SO2 and separated by at least two carbon atoms;

R1 is selected from H, (C1-3)alkyl, haloalkyl;

Each **R2** and **R3** is independently selected from H, halogen (preferably fluorine), alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkylaryl, alkyl-heteroaryl, heteroalkyl-aryl, heteroalkyl-heteroaryl, aryl-alkyl, aryl-heteroalkyl, heteroaryl-alkyl, heteroaryl-heteroalkyl, aryl-aryl, aryl-heteroaryl, heteroaryl-aryl, heteroaryl-heteroaryl, cycloalkyl-alkyl, heterocycloalkyl-alkyl, alkyl-cycloalkyl, alkyl-heterocycloalkyl;

Each **R4** is independently selected from H, halogen (preferably fluorine), (C1-3)alkyl or haloalkyl;

R6 is selected from H, alkyl, heteroalkyl, heterocycloalkyl, aryl, heteroaryl, alkylaryl, alkyl-heteroaryl, heteroalkyl-aryl, heteroalkyl-heteroaryl, arylalkyl, aryl-heteroalkyl, heteroaryl-alkyl, heteroaryl-heteroalkyl, aryl-aryl, aryl-heteroaryl, heteroaryl-aryl, heteroaryl-heteroaryl;

Each of the **R2, R3** and **R6** radicals may be independently optionally substituted with one or more (preferably one) groups selected from alkyl, heteroalkyl, aryl, heteroaryl, halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, thiol, alkylthiol, arylthiol, alkylsulfon, haloalkylsulfon, arylsulfon, aminosulfon, N-alkylaminosulfon, N,N-dialkylaminosulfon, arylaminosulfon, amino, N-alkylamino, N,N-dialkylamino, amido, N-alkylamido, N,N-dialkylamido, cyano, sulfonamino, alkylsulfonamino, arylsulfonamino, amidino, N-aminosulfon-amidino, guanidino, N-cyano-guanidino, thioguanidino, 2-nitro-ethene-1,1-diamin, carboxy, alkyl-carboxy, nitro, carbamate;

Optionally **R2** and **R3** may join to form a ring comprising up to 7 ring atoms, or R2 and R4 may join to form a ring comprising up to 7 ring atoms, or R2 and R6 may join to form a ring comprising up to 7 ring atoms, or R3 and R4 may join to form a ring comprising up to 7 ring atoms, or R3 and R6 may join to form a ring comprising up to 7 ring atoms, or R4 and R6 may join to form a ring comprising up to 7 ring atoms;

R5 is a monocyclic, bicyclic or tricyclic group comprising one, two or three ring structures each of up to 7 ring atoms independently selected from cycloalkyl, aryl, heterocycloalkyl or heteroaryl, with each ring structure being independently optionally substituted by one or more substituents independently selected from halogen, hydroxy, alkyl, alkoxy, haloalkoxy, amino, N-alkylamino, N,N-dialkylamino, alkylsulfonamino, alkylcarboxyamino, cyano, nitro, thiol, alkylthiol, alkylsulfonyl, haloalkylsulfonyl, alkylaminosulfonyl, carboxylate, alkylcarboxylate, aminocarboxy, N-alkylamino-carboxy, N,N-dialkylamino-carboxy, wherein any alkyl radical within any substituent may itself be optionally substituted with one or more groups selected from halogen, hydroxy, alkoxy, haloalkoxy, amino, N-alkylamino, N,N-dialkylamino, N-alkylsulfonamino, N-alkylcarboxyamino, cyano, nitro, thiol, alkylthiol, alkylsulfonyl, N-alkylaminosulfonyl, carboxylate, alkylcarboxy, aminocarboxy, N-alkylaminocarboxy, N,N-dialkylaminocarboxy, carbamate;

when **R5** is a bicyclic or tricyclic group, each ring structure is joined to the next ring structure by a direct bond, by -O-, by (C1-6)alkyl, by (C1-6)haloalkyl, by (C1-6)heteroalkyl, by (C1-6)alkenyl, by (C1-6)alkynyl, by sulfone, by CO, by NCO, by CON, by NH, by S, by C(OH) or is fused to the next ring structure;

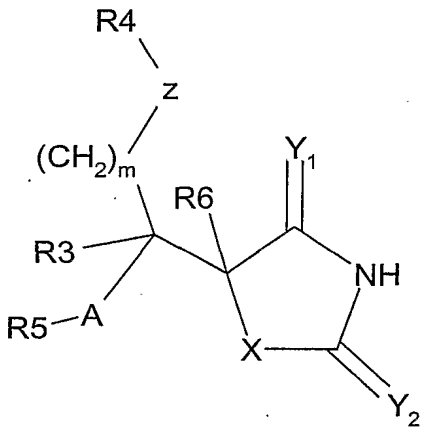
R7 is selected from (C1-6) alkyl, (C3-7)cycloalkyl, (C2-6)heteroalkyl, (C2-6)cycloheteroalkyl;

Any heteroalkyl group outlined above is a hetero atom-substituted alkyl containing one or more hetero groups independently selected from N, O, S, SO, SO2, (a hetero group being a hetero atom or group of atoms);

Any heterocycloalkyl or heteroaryl group outlined above contains one or more hetero groups independently selected from N, O, S, SO, SO2;

Any alkyl, alkenyl or alkynyl groups outlined above may be straight chain or branched; unless otherwise stated, any alkyl group outlined above is preferably (C1-7)alkyl and most preferably (C1-6)alkyl.

A compound of formula III



III

wherein

X is selected from NR1, O, S;

Y1 and **Y2** are independently selected from O, S;

Z is selected from NR2, O, S;

m is 0 or 1;

A is selected from a direct bond, (C1-6)alkyl, (C1-6) alkenyl, (C1-6)haloalkyl, or (C1-6)heteroalkyl containing a hetero group selected from N, O, S, SO, SO2 or containing two hetero groups selected from N, O, S, SO, SO2 and separated by at least two carbon atoms;

R1 is selected from H, alkyl, haloalkyl;

R2 is selected from H, alkyl, haloalkyl;

R3 and **R6** are independently selected from H, halogen (preferably F), alkyl, haloalkyl, alkoxyalkyl, heteroalkyl, cycloalkyl, aryl, alkyl-cycloalkyl, alkyl-heterocycloalkyl, heteroalkyl-cycloalkyl, heteroalkyl-heterocycloalkyl, cycloalkyl-alkyl, cycloalkyl-heteroalkyl, heterocycloalkyl-alkyl, heterocycloalkyl-heteroalkyl, alkylaryl, heteroalkyl-aryl, heteroaryl, alkylheteroaryl, heteroalkyl-heteroaryl, arylalkyl, aryl-heteroalkyl, heteroaryl-alkyl, heteroaryl-heteroalkyl, bisaryl, aryl-heteroaryl, heteroaryl-aryl, bisheteroaryl, cycloalkyl or heterocycloalkyl comprising 3 to 7 ring atoms, wherein the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl or heterocycloalkyl radicals may be optionally substituted by one or more groups independently selected from hydroxy, alkyl,

heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, hydroxyalkyl, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, carboxy, carboxyalkyl, alkylcarboxy, amino, N-alkylamino, N,N-dialkylamino, alkylamino, alkyl(N-alkyl)amino, alkyl(N,N-dialkyl)amino, amido, N-alkylamido, N,N-dialkylamido, alkylamido, alkyl(N-alkyl)amido, alkyl(N,N-dialkyl)amido, alkylcarbamate, alkylcarbamide, thiol, sulfone, sulfonamino, alkylsulfonamino, arylsulfonamino, sulfonamido, haloalkyl sulfone, alkylthio, arylthio, alkylsulfone, arylsulfone, aminosulfone, N-alkylaminosulfone, N,N-dialkylaminosulfone, alkylaminosulfone, arylaminosulfone, cyano, alkylcyano, guanidino, N-cyano-guanidino, thioguanidino, amidino, N-aminosulfon-amidino, nitro, alkylnitro, 2-nitro-ethene-1,1-diamine;

R4 is selected from H, alkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, haloalkoxy, aminoalkyl, amidoalkyl, thioalkyl;

R5 is a monocyclic, bicyclic or tricyclic group comprising one, two or three ring structures each of 3 to 7 ring atoms independently selected from cycloalkyl, aryl, heterocycloalkyl or heteroaryl, with each ring structure being independently optionally substituted by one or more substituents independently selected from halogen, thiolo, thioalkyl, hydroxy, alkylcarbonyl, haloalkoxy, amino, N-alkylamino, N,N-dialkylamino, cyano, nitro, alkyl, haloalkyl, alkoxy, alkyl sulfone, alkylsulfonamido, haloalkyl sulfone, alkylamido,alkylcarbamate, alkylcarbamide, carbonyl, carboxy, wherein any alkyl radical within any substituent may itself be optionally substituted by one or more groups independently selected from halogen, hydroxy, amino, N-alkylamino, N,N-dialkylamino, alkylsulfonamino, alkylcarboxyamino, cyano, nitro, thiol, alkylthiol, alkylsulfono, alkylaminosulfono, alkylcarboxylate, amido, N-alkylamido, N,N-dialkylamido, alkylcarbamate, alkylcarbamide, alkoxy, haloalkoxy, carbonyl, carboxy;

when **R5** is a bicyclic or tricyclic group, each ring structure is joined to the next ring structure by a direct bond, by -O-, by –S-, by-NH-, by (C1-6)alkyl, by (C1-6)haloalkyl, by (C1-6)heteroalkyl, by (C1-6)alkenyl, by (C1-6)alkynyl, by sulfone, by carboxy(C1-6)alkyl, or is fused to the next ring structure;

Optionally **R2** and **R4** may join to form a ring comprising up to 7 ring atoms or R3 and R6 may join to form a ring comprising up to 7 ring atoms;

Any heteroalkyl group outlined above or below is a hetero atom-substituted alkyl containing one or more hetero groups independently selected from N, O, S, SO, SO2, (a hetero group being a hetero atom or group of atoms);

Any heterocycloalkyl or heteroaryl group outlined above or below contains one or more hetero groups independently selected from N, O, S, SO, SO2; Any alkyl, alkenyl or alkynyl groups outlined above or below may be straight chain or branched; unless otherwise stated, any alkyl group outlined above is preferably (C1-7)alkyl and most preferably (C1-6)alkyl.

It will be appreciated that the particular substituents and number of substituents in metalloproteinase inhibitor compounds for use according to the invention are selected so as to avoid sterically undesirable combinations.

Each exemplified compound represents a particular and independent aspect of the invention.

Where optically active centres exist in the compounds, we disclose all individual optically active forms and combinations of these as individual specific embodiments of the invention, as well as their corresponding racemates. Racemates may be separated into individual optically active forms using known procedures (cf. Advanced Organic Chemistry: 3rd Edition: author J March, p104-107) including for example the formation of diastereomeric derivatives having convenient optically active auxiliary species followed by separation and then cleavage of the auxiliary species.

It will be appreciated that the compounds may contain one or more asymmetrically substituted carbon atoms. The presence of one or more of these asymmetric centres (chiral centres) in a compound can give rise to stereoisomers, and in each case the invention is to be understood to extend to the use of all such stereoisomers, including enantiomers and diastereomers, and mixtures including racemic mixtures thereof.

Where tautomers exist in the compounds of the invention, we disclose all individual tautomeric forms and combinations of these as individual specific embodiments of the invention.

The invention provides a metalloproteinase inhibitor compound or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof for use in the treatment of a disease or condition mediated by one or more metalloproteinase enzymes wherein the metalloproteinase inhibitor compound is a compound of formula II or a compound of formula III.

The invention further provides a method of treating a metalloproteinase mediated disease or condition which comprises administering to a warm-blooded animal a therapeutically effective amount of a metalloproteinase inhibitor compound or a pharmaceutically acceptable salt or or in vivo hydrolysable ester thereof wherein the metalloproteinase inhibitor compound is a compound of formula II or a compound of formula III.

In yet a further aspect the invention provides the use of a metalloproteinase inhibitor compound or a pharmaceutically acceptable salt or or in vivo hydrolysable ester thereof in the preparation of a medicament for use in the treatment of a disease or condition mediated by one or more metalloproteinase enzymes, wherein the metalloproteinase inhibitor compound is a compound of formula II or a compound of formula III.

In another aspect the invention provides a pharmaceutical composition for use in the treatment of a disease or condition mediated by one or more metalloproteinase enzymes which comprises a metalloproteinase inhibitor compound or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof and pharmaceutically acceptable carrier, wherein the metalloproteinase inhibitor compound is a compound of formula II or a compound of formula III.

In another aspect the invention provides a method of treating a metalloproteinase mediated disease or condition which comprises administering to a warm-blooded animal a therapeutically effective amount of a pharmaceutical composition which comprises a metalloproteinase inhibitor compound or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof and pharmaceutically acceptable carrier, wherein the metalloproteinase inhibitor compound is a compound of formula II or a compound of formula III.

Preparation of the metalloproteinase inhibitor compounds of formula II

Compounds of the formula II or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, may be prepared by processes described in (a) to (h) below. It will be appreciated that many of the relevant starting materials are commercially or otherwise available or may be synthesised by known methods or may be found in the scientific literature.

Compounds of formula II are exemplified in Examples 1 to 23. Compounds wherein Z is selected from $SO_2N(R6)$, $N(R7)SO_2$, $N(R7)SO_2N(R6)$ are shown in Examples 1 to 5. Compounds wherein Z is selected from SO, SO_2 are shown in Examples 6 to 20. Compounds wherein Z is selected from O, S are shown in Examples 21 to 23.

(a) Compounds of formula II in which Y1 and Y2 are each O, Z is SO2N(R6), A is a direct bond, X is NR1, R1 is H, R2 is H, m is 1, R3 is H, R4 is H, and R5 and R6 are defined as in formula II may be prepared according to Scheme 1.

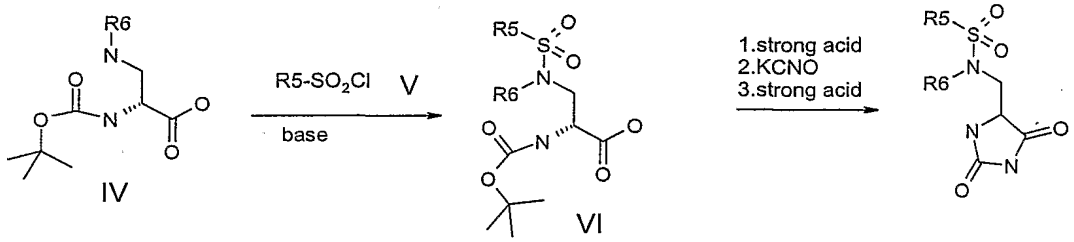
When R6 is H, an N^1-BOC-D-diaminopropionic acid derivative of formula IV is reacted with suitable sulfonyl chloride of formula V in basic medium to form sulfonamides

of formula VI. Deprotection in acid medium, reaction with potassium cyanate to the corresponding urea and finally cyclization in acid medium yields compounds of formula II.

When R6 is alkyl such as methyl, ethyl, propyl, isopropyl and n-butyl, the N^2 –alkyl-N^1-BOC-D-diaminopropionic acid of formula IV is prepared according to Andruszkiewics, R.: *Pol.J.Chem,* **62**,257, (1988).

When R6 is an optionally substituted benzyl, methylbenzyl, methylpyridyl, methyl heteroaryl, the N^2-substituted amino acid of formula IV is prepared according to *Helv.Chim.Acta,* **46**,327, (1963).

Scheme 1:



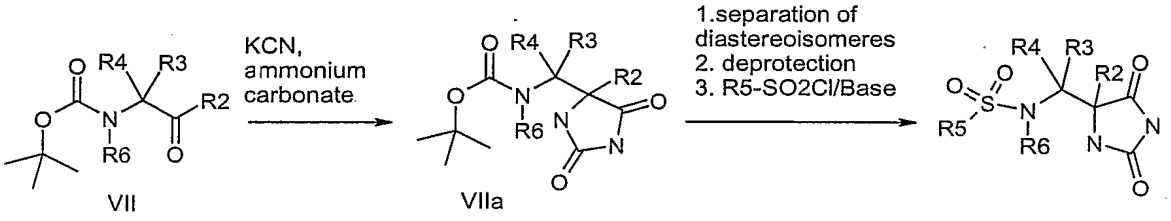
The reaction IV-VI is preferably performed in suitable solvent optionally in the presence of base for 1 to 24h at ambient to reflux temperature. Preferably, solvents such as pyridine, dimethylformamide, tetrahydrofurane, acetonitrile or dichlorometane are used with bases like triethylamine, N-methylmorpholine, pyridine or alkali metal carbonates at ambient temperature for 2-16 h reaction time, or until end of reaction is achieved as detected by chromatographic or spectroscopic methods. Reactions of sulfonyl chlorides of formula V with various secondary amines are previously described in the literature, and the variations of the conditions will be evident for those skilled in the art. A variety of compounds of formula V are commercially available or their synthesis is described in the literature. Specific derivatives of formula VI may be made according to known processes by those skilled in the art.

(b) Compounds of formula II in which Y1 and Y2 are each O, Z is SO2N(R6), R6 is H, A is a direct bond, X is NR1, R1 is H, m is 1, and R2, R3, R4 and R5 are defined as in formula II may be prepared according to Scheme 1.

Compounds in which R2 is H, R3 is H and R4 is alkyl or aryl, may be prepared starting from the corresponding BOC N-protected α-amino aldehydes of formula VII, prepared according to *Fehrentz,JA,Castro,B.;* Synthesis, 676, (1983).

Compounds in which R2 is alkyl or aryl, R3 is H and R4 is alkyl or aryl, may be prepared starting from the corresponding BOC N-protected α-amino ketone of formula VII as depicted in Scheme 2., The BOC N-protected α-amino ketones are prepared according to *Nahm,S, Weinreb,SM:* Tetrahedron Lett.**22**,3815,(1981), optionally when R6 is not H, according to *Shuman, Robert T.* US 4448717 A 19840515

Scheme 2:



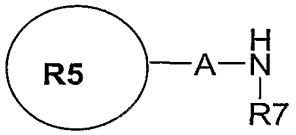
The compounds of formula VII are reacted with alkali cyanide and ammonium carbonate (*Strecker reaction*) to yield the corresponding hydantoins of formula VIIa. The diastereoisomeres can optionally be separated after any of the three remaining synthetic steps: carbamates of formula VIIa and sulfonamide compounds of formula II on silicagel chromatography, after deprotection amino intermediate by chrystallisation. The amine intermediates are optionally used to directly couple with sulfonyl chlorides of formula V as described in the sulfonylation in (a) above, in basic medium to form compounds of formula II.

The reaction VII to VIIa is preferably run in a closed steel vessel in an aqueous alcohol solvent at 90-130°C for 3-16 hours or until end of reaction is achieved as detected by chromatographic or spectroscopic methods. Treatment with 1-4 fold excess cyanide

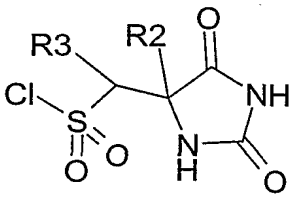
salts, preferrably 1-2 equivalents, and 2-6 fold excess of ammonium carbonate, preferrably 4-6 equivalents yields hydantoins of formula VIIa. Deprotection and sulfonylation as in Scheme 1 then yields compounds of formula II.

Amino aldehydes or ketones of formula VII and their protected derivatives are commercially available and other methods to α-amino aldehydes and ketones of formula VII. Specific derivatives of formula VIIa may be made according to known processes by those skilled in the art.

(c) Compounds of formula II in which Y1 and Y2 are each O, X is NR1 (R1=H), Z=N(R7)SO2, m=1, R4=H and R2, R3, R5 and R7 are as defined in formula II may be prepared by reacting a compound of formula VIII in which R2, R3, R5,R7 and A are as described in formula II, with sulfonyl chlorides of formula IX in polar aprotic solvents such as THF or DMF in the presence of bases such as alkali carbonates or tertiary alkyl amines or polymeric amines.

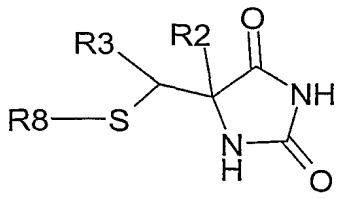


VIII

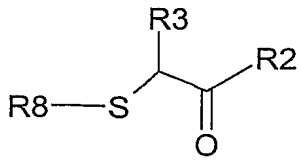


IX

Amines of formula VIII are well known in the literature and are available from numerous commercial sources. Specific new variations of compounds of formula VIII may be made according to known processes by those skilled in the art. The sulfonyl chlorides of formula IX may be prepared by chlorine oxidation of sulfides or disulfides of formula X, where R8 is a group such as hydrogen, isopropyl, benzyl or a sulfide such that formula X comprises of a symmetrical disulfide.



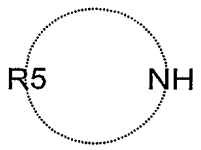
X



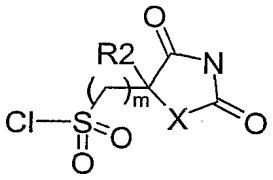
XI

Sulfides of formula X may be made from cysteine or cystine (R2, R3=H) and their esters by sequential treatment with alkali cyanate and strong acids like potassium cyanate and hydrochloric acid. Alternatively, sulfides of formula X may be prepared by subjecting ketones of formula XI to conditions as described in the transformation of VII to VIIa above in (a).

(d) Compounds of formula II in which Y1 and Y 2 are each O, Z is SO_2, R2 is as defined in formula II, A is a direct bond and R5 comprises a nitrogen directly attached to Z, or A is (C1-6) N-alkyl, may be prepared by reacting a compound of the formula IVb in which R5 is defined as in formula II with the known compounds of the formula Vb in which X and m are as defined in formula II:



IVb

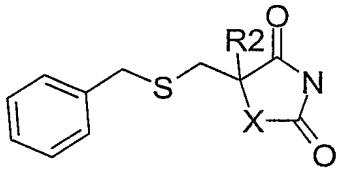


Vb

The reaction is preferably performed in suitable solvent optionally in the presence of base for 1 to 24h at ambient to reflux temperature. Preferably, solvents such as pyridine, dimethylformamide, tetrahydrofurane, acetonitrile or dichlorometane are used with bases like triethylamine, N-methylmorpholine, pyridine or alkali metal carbonates at ambient temperature for 2-16 h reaction time, or until end of reaction is achieved as detected by chromatographic or spectroscopic methods. Reactions of sulfonyl chlorides of formula Vb with various primary and secondary amines are previously described in the literature, and the variations of the conditions will be evident for those skilled in the art.

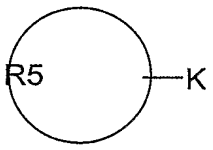
Synthesis of compounds of formula Vb is described in the literature and can be prepared from e.g. cystein or homocystein (Mosher,J.:J.Org.Chem.**23**,1257 (1958).

Sulfonylchlorides of formula Vb, in which m=1, X=NR1(R1=H) and R2 is as described in formula II, are conveniently prepared by oxidative chlorination of compounds of formula Va, in which R2 is as described in formula II (Griffith, O.: J. Biol. Chem., 1983, 258, 3, 1591).

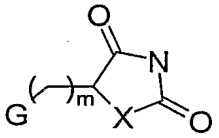


Va

(e) Compounds of formula II in which Y1 and Y2 are each O, Z is S or O, and X and R5 are as described in formula II may be prepared by reacting a compound of formula VIb in which K is a leaving group (e.g chloride, or sulfonate ester) and R5 as described in formula II,



VIb



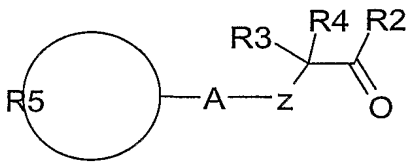
VIIb

with a compound of formula VIIb, in which G is a sulfhydryl (SH), X and m as described in formula II. The reaction is preferably performed in the presence of base such as diethyl isopropyl amine or cesium carbonate and in the presence of a suitable solvent e.g DMF.

Alternatively, the compounds under process (e) may be prepared in the same manner as in process (e), by reacting the compounds of formula VIb and VIIb, but in which K in compound VIb is the sulfhydryl (SH) or a hydroxyl group and G in formula VIIb represents a leaving group.

(f) Compounds of the formula II in which Y1 and Y2 are each O, Z is SO2 or S(O), and X, A , and R5 are as described in formula II, may be prepared by oxidizing the final products described under process (e) and in which Z is S, with oxidizing agents like peroxide reagents, preferably m-chloroperbenzoic acid or oxone.

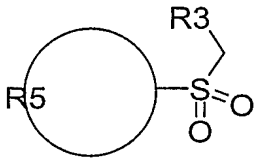
(g) Compounds of the formula II in which Y1 and Y2 are each O, X is NR1(R1=H), m is 1, and R2, R3, R4, R5 are as described in formula II may be prepared by reacting a compound of formula XIb in which R2, R3, R4, R5 and A are as described in formula II,



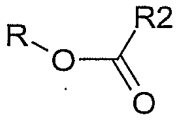
XIb

with ammonium and cyanide salts in protic solvents, preferably in the presence of excess ammonium carbonat and potassium cyanide in ethanol in a sealed vessel at 40-80 C for 4-24 hours.

The ketones of formula XIb are conveniently prepared by treating sulfonamides of formula XII in which R3 is H and R5 is as described in formula II, with excess strong base and then treatment with esters of formula XIII , in which R is an alkyl or aryl residue and R2 are as described for formula II, in non-protic solvents. Preferrable conditions are 2-3 equivalents of lithium bases like lithium diisopropylamide or lithium hexamethyldisilazane or butyl lithium in dried etheral solvents like tetrahydrofurane.

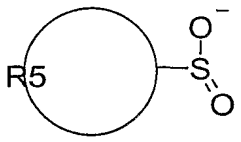


XII

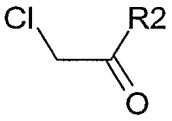


XIII

The ketones of formula XIb, in which R3 and R4 are each alkyl or form a ring, R5 is aryl or heteroaryl and R2 is alkyl or aryl, can also be prepared by treating sulfinates of formula XIV in which R5 is aryl or heteroaryl as described in formula II, with a base such as tetrabutylammonium bromide and a ketone of formula XV in which R2 is alkyl or aryl (Crandall *et al* J. Org. Chem. 1985, (8) 50, 1327-1329). R3 and R4 are then introduced by reaction with alkyl halides or alkyl dihalides. The reaction is preferably performed in the presence of base such as potassium carbonate or caesium carbonate and in the presence of a suitable solvent e.g. DMF or DMSO at 50-100°C.

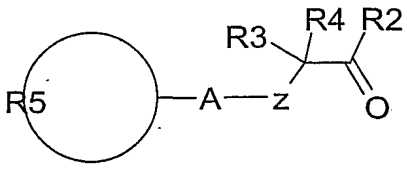


XIV



XV

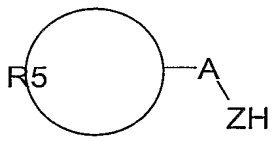
(h) Compounds of formula II in which Y1 and Y2 are each O, X is NR1(R1=H), Z is S or O, and R2, R3, R4, R5 are as described in formula II may be prepared by reacting a compound of formula VIIIc in which R2, R3, R4, R5 and A are as described in formula II,



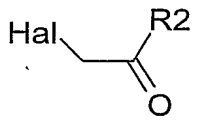
VIIIc

with ammonium and cyanide salts in protic solvents, preferably in the presence of excess ammonium carbonat and potassium cyanide in ethanol in a sealed vessel at 40-80 C for 4-24 hours.

The ketones of formula VIIIc are conveniently prepared by treating alcohols or thiols of formula IXc, in which R5 and A are as described in formula II, with haloketones of formula Xc , in which R2 is as described for formula II, and excess base.



IXc



Xc

Preparation of the metalloproteinase inhibitor compounds of formula III

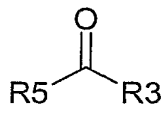
Compounds of the formula III or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, may be prepared by processes described in (a) to (h) below. It will be appreciated that many of the relevant starting materials are commercially or otherwise available or may be synthesised by known methods or may be found in the scientific literature. (X, Y1, Y2, Z, m, A and R1-R6 are as hereinbefore defined for the compound of formula III).

Compounds of formula III are exemplified in Examples 24 to 61. Compounds wherein R5 is a bicyclic or tricyclic group are shown in Examples 24 to 39. Compounds wherein R5 is a monocyclic group are shown in Examples 40 to 61. If not stated otherwise commercially available starting materials or intermediates described in Table 2 and 3 were used.

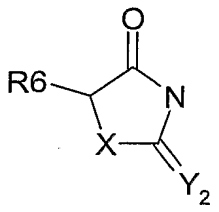
(a) A compound of the formula III may be converted to a salt, especially a pharmaceutically acceptable salt, or vice versa, by known methods; a salt, especially a pharmaceutically acceptable salt, of a compound of the formula III may be converted into a different salt, especially a pharmaceutically acceptable salt, by known methods.

(b) Compounds of the formula III in which Z= O and R4= H may be prepared by reacting a compound of the formula IIa with a compound of the formula IIIa or a suitably protected form of a compound of formula IIIa (as shown in Scheme 1), and optionally thereafter forming a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof:

Scheme 1



IIa



IIIa

Aldehydes or ketones of formula IIa and compounds of formula IIIa in a suitable solvent are treated with a base, preferably in the temperature range from ambient temperature to reflux. Preferred base-solvent combinations include aliphatic amines such as trimethylamine, pyrrolidine or piperidine in solvents such as methanol, ethanol, tetrahydrofurane, acetonitrile or dimethylformamide, with addition of water when necessary to dissolve the reagents (Phillips, AP and Murphy, JG, 1951, J. Org. Chem. 16); or lithiumhexamethyldisilazan in tetrahydrofurane (Mio, S *et al,* 1991, Tetrahedron 47:2121-2132); or barium hydroxide octahydrate in isopropanol-water (Ajinomoto KK, 1993, Japanese Patent Number 05097814).

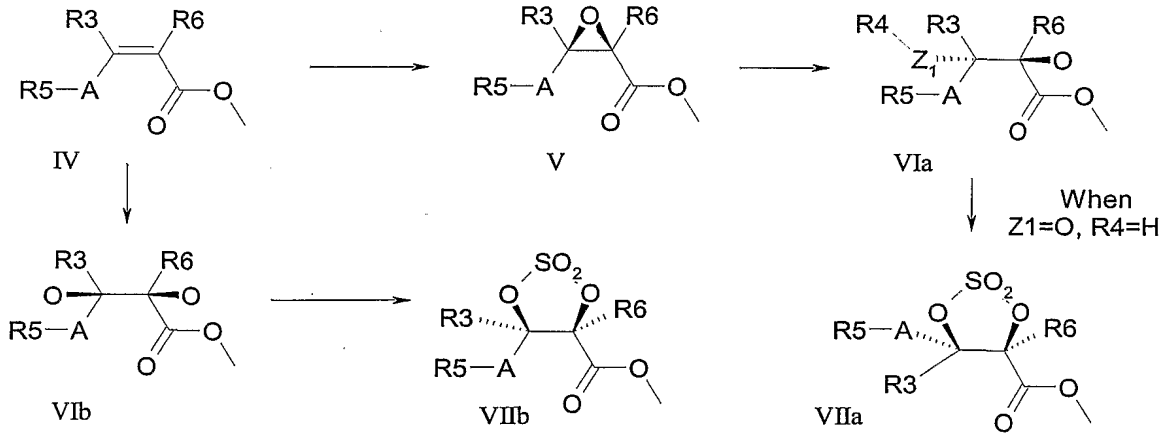
Preferably, when preparing compounds of the formula III by this process, R3, R5 or R6 will not contain additional functionalities such as aldehydes, ketones, halogenated radicals or any other radicals well known to those skilled in the art which have the potential of interfering with, competing with or inhibiting the bond formation reaction.

It will be appreciated that many of the relevant starting materials are commercially or otherwise available or may be synthesised by known methods or may be found in the scientific literature.

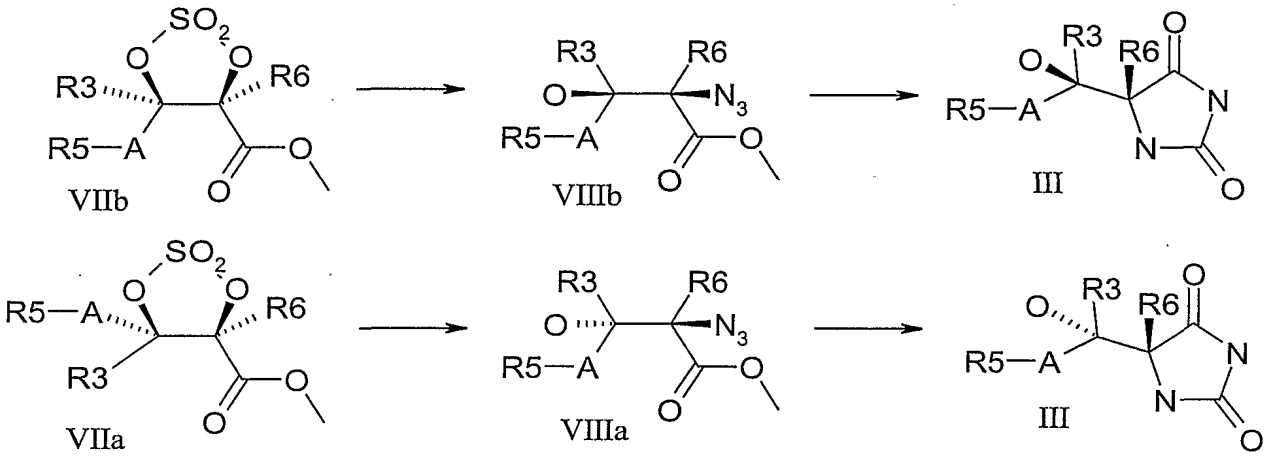
To prepare compounds of the general formula IIIa (R6 as hereinbefore described), compounds of formula IIIa in which R6 is H may be reacted with an appropriate aldehyde or ketone followed by dehydration and subsequent reduction of the resulting double bond by methods which are well know to those skilled in the art.

(c) Compounds of the formula III in which Z = O, R4 = H and X= N or NR1, especially specific stereoisomers thereof, may also be prepared as described for two of the four possible stereoisomers in Schemes 2 and 3 below.

Scheme 2



Scheme 3



Starting from the propenoate derivatives of formula IV, via the diols VIa or VIb by either asymmetric epoxidation followed by regioselective opening with water, or asymmetric dihydroxylation. Depending on the chiral auxiliary in the epoxidation or dihydroxylation, either the shown stereoisomers or their enantiomers of the diols of formula VIa or VIb can be obtained. (For example, Ogino, Y. *et al,* 1991, Tetrahedron Lett. 32 (41):5761-5764; Jacobsen, E. N. *et al*, 1994, Tetrahedron, 50(15):4323-4334; Song, C. E. *et al, 1997,* Tetrahedron Asymmetry, 8 (6):841-844). Treatment with organic base and thionyl chloride and subsequent ruthenium tetroxide catalysed oxidation yields the cyclic sulfates VIIa and VIIb.

The cyclic sulfates of formula VIIa and VIIb are converted to the hydroxy azides (Scheme 3) of formula VIIIa and VIIIb by treatment with sodium azide in dimethylformamide followed by careful hydrolysis of the hemisulfate intermediates before aqueous work-up. (Gao, Sharpless, 1988, J.Am.Chem.Soc., 110:7538; Kim, Sharpless, 1989, Tetrahedron Lett., 30:655). The hydroxy azides of formula VIIIa and VIIIb are hydrolysed and reduced to the β-hydroxy-α-amino acids (not shown in Scheme 3), preferably hydrolysis with LiOH in THF followed by reduction with hydrogen sulfide, magnesium in methanol or organic phosphines by the Staudinger procedure. The β-hydroxy-α-amino acids in turn yield compounds of formula III upon treatment with cyanate and acid in aqueous media.

(d) Compounds of the formula III in which Z =O and R4 is not H, especially specific stereoisomers thereof, may also be prepared as described for two of the four possible stereoisomers in Schemes 2 and 3. The compounds may be prepared by reacting the epoxides of formula V in Scheme 2 with an alcohol of formula R4-OH, yielding the alcohols VIa. Subsequent conversion to the azides with phosphoazidate (Thompson, A. S. *et al,* 1993, J. Org. Chem. 58(22):5886-5888) yields the ether analogs of the azido esters VIIIa in Scheme 3, which can be carried through to the final products as described under process (c). The radical R4 in alcohols R4-OH and the radicals R3, R5 and R6 in may be suitably protected. The protecting groups can be removed as a last step after the conversion to the hydantoins of formula III.

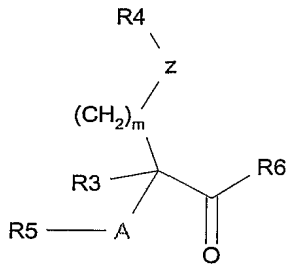
(e) Compounds of the formula III in which Z is S or NR2 and Y1 and/or Y2 is O, especially specific stereoisomers thereof, may also be prepared as described for two of the four possible stereoisomers in Schemes 2 and 3. The compounds may be synthesised by opening of the epoxides of formula V (Scheme2) with thiols R4-SH or amines R4-NH_2 and thereafter subjected to analogous transformations as described for the alcohols VIIIa and VIIIb in Scheme 3. When amines of R4-NH2 are used, it may be necessary to N-protect the intermediate amino alcohols, especially when the radical R4 is a n-alkyl group.

(f) Compounds of the formula III in which X is S and Y1 and/or Y2 is O, especially specific stereoisomers thereof, may also be prepared as described for two of the four possible stereoisomers in Schemes 2 and 3. The compounds may be prepared by reacting the cyclic sulfates of formula VIIa or VIIb, or the α-hydroxy esters of formula VIa via their sulfonate esters, with thiourea and acid (1997, Japanese Patent number 09025273).

The propenoate derivatives of formula IV are widely accessible, eg from aldehydes and phosphonium or phosphonate derivatives of acetic acid via the Wittig or Horner-Emmons reaction (for example, van Heerden, P. S. *et al*, 1997, J. Chem. Soc., Perkin Trans. 1(8):141-1146).

(g) Compounds of the formula III in which X=NR1 and R1=H may be prepared from reacting an appropriate substituted aldehyde or ketone of formula IId with ammonium

carbonate and potassium cyanide in aqueous alcohols at 50-100°C in a sealed vessel for 4-24h.



IId

Preparations of some aldehydes or ketones of formula IId are described in:

Marte, A.-M. *et al*, Tetrahedron Lett., 1990, 31(18):2599-2602;

Kren, V. *et* al, 1993, J. Chem. Soc., Chem. Commun., 4:341-343;

Schmittel, M. *et al*, 1990, Angew. Chem., 102(10):1174-1176;

Chakraborty, R. *et al*, 1992, Synth. Commun., 22(11):1523;

Harder, T. *et al*,1994, Tetrahedron Lett., 35(40):7365-7368;

Ruder, S. M., 1992, Tetrahedron. Lett., 33(9):2621 - 2624;

Maeda, H. *et al*, 1997, Chem. Pharm. Bull., 45(11):1729-1733;

Montana, J. G. *et* al, 1994, J. Chem. Soc., Chem. Commun., 19:2289-2290;

Davis, B. R. *et al*, 1992, Aust. J. Chem. 45(5):865 – 875.

Some of the aldehydes or ketones are available through aldol reactions (m=1, Z=O):

Mahrwald, R, *et al*, 1998, J. Am. Chem. Soc., 120(2):413-414;

Auerbach, R. A., *et al*, 1988, Org. Synth., VI:692;

Mukaiyama, T.; 1977, Angew. Chem., (Int. Ed.) 16;

Shimizu, N. *et al*, 1983, Bull. Chem. Soc. Jpn., 56(12):853;

Maruoka, K. *et al*, 1986, J. Am. Chem. Soc., 108(13):3827.

Known preparation of compounds of formula IId are listed in Table 1 below:

Table 1

Name (formyl 1st, even when "non IUPAC")	CAS number
2-formyl-5-pyridin-3-yl furane	38588-49-7
2-formyl-5-pyridin-2-y furane	55484-36-1
5-formyl-2-phenyl oxazole	92629-13-5
2-formyl-5-phenyl furane	13803-39-9
2-formyl-3-methyl-5-phenyl furane	160417-25-4
2-formyl-3-ethoxycarbonyl furane	50800-39
2-formyl-5-phenyl-3,4-oxadiazole	22816-01-9
2-formyl-5-phenyl oxazole	96829-89-9
2-formyl-4-chloro-5-phenyl oxazole	119344-57-9
2-formyl-4-chloro-2-pyridin-3-yl thiazole	131969-58-9
2-formyl-5-pyridin-3-yl thiophene	133531-43-8
2-formyl-5-pyridin-2-yl thiophene	132706-12-8
2-formyl-5-pyridin-4-yl thiophene	21346-36-1
5-formyl-2-phenyl thiazole	1011-40-1
5-formyl-4-chloro-2-phenyl thiazole	108263-77-0
5-formyl-4-methyl-2-phenyl thiazole	55327-23-6
2-formyl-5-phenyl thiophene	19163-21-4
2-formyl-3-methyl-5-phenyl thiophene	1604417-30-1
4-formyl-2-pyridin-2-yl imidazole	279251-08-0
2-formyl-1-methyl-5pyridin-3-yl pyrrole	3614-77-5
4-formyl-2-pyridin-3-yl imidazole	279251-09-1
4-formyl-2-pyridin-4-yl 1,3,4-triazole	42786-73-2
4-formyl-2-pyridin-4-yl imidazole	279251-10-4
4-formyl-5-methoxy-5-phenyl thiazole	73725-36-7
4-formyl-5-ethoxycarbonyl-5-phenyl thiazole	88469-73-2
4-formyl-5-ethoxycarbonyl-5-phenyl oxazole	189271-85-0

2-formyl-3methyl-5-phenyl 1,3,4-triazole	89060-36-6
4-formyl-1-methyl-2-phenyl imidazole	94938-02-0
5-formyl-1-methyl-2-phenyl imidazole	94938-03-1
4-formyl-1-butyl-2-phenyl imidazole	198066-02-3
4-formyl-1-propyl-2-phenyl imidazole	75378-63-1
5-formyl-1-butyl-2-phenyl imidazole	198065-92-8
2-formyl-1-methyl-4-phenyl imidazole	123511-51-3
4-formyl-2-phenyl-5-methyl oxazole	70170-23-9
2-formyl-5-phenyl 1,3,4-triazole	26899-64-9
4-formyl-2-phenyl-5-chloro imidazole	60367-52-4
4-formyl-2-phenyl imidazole	68282-47-3
4-formyl-2-phenyl-5-methyl imidazole	68282-50-8
2-formyl-1-methyl-5-phenyl 1,3,4-triazole	219600-03-0
2-formyl-4-phenyl imidazole	56248-10-3
2-formyl-1-methyl-4-phenyl imidazole	118469-06-0
2-formyl-5-phenyl pyrazole	52179-74-5
2-formyl-3-methyl-5-phenyl pyrazole	160417-28-7
2-formyl-3-ethoxycarbonyl-5-phenyl pyrazole	63202-77-7
2-formyl-5-morfolin-1-yl furane	3680-96-4
2-formyl-5-piperdin-1-yl furane	22868-60-6
2-formyl-5-cyclohexyl furane	14174-51-7
2-formyl-3-methyl-5-cyclohexyl furane	160417-27-6

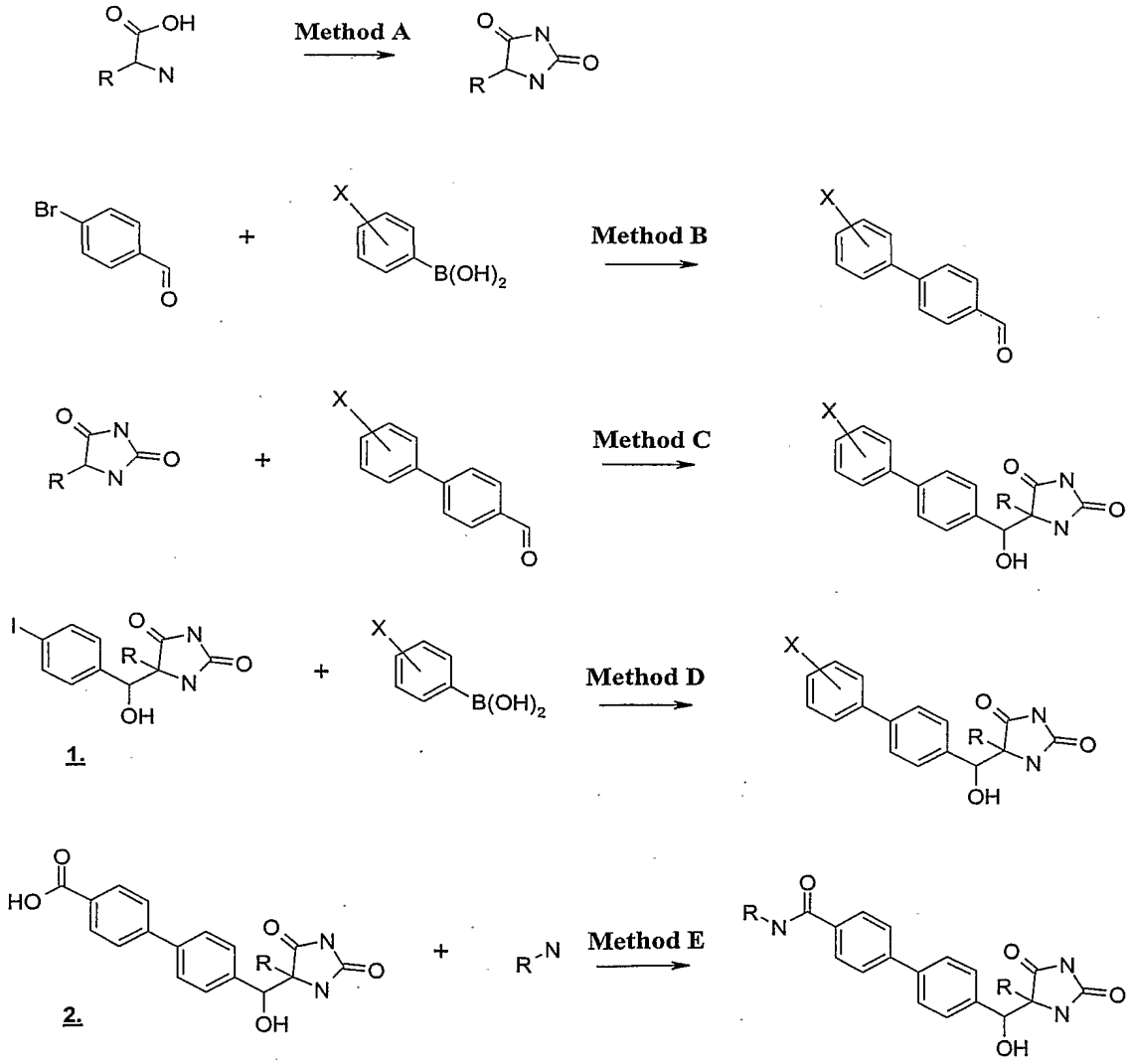
(h) Compounds of the formula III may also be synthesized according to Scheme 4 below. Suitable target compounds include the substituted 5-(biphenyl-4-yl-hydroxy-methyl)-imidazolidie-2,4-dione series and the substituted 5-[4-phenoxy-phenyl]-hydroxy-methyl -imidazolidine-2,4-dione series.

The key reaction is the aldol condensation (Method C) that forms the target compounds. The synthetic intermediates in this reaction are the 5-hydantoins, made from

amino acids (Method A), and the aldehydes prepared through a Suzuki coupling (Method B) in a conventional manner. Method C also produces compounds 1. and 2. which may be utilized for further transformations, a Suzuki coupling (Method D) and amide coupling (Method E).

The aldol condensation gives a diastereomeric mixture. The racemates are isolated by chromatography or in some cases by crystallization. The enantiomeres may be resolved by chiral chromatography.

Scheme 4



The metalloproteinase inhibitor compounds may be evaluated for example in the following assays:

Isolated Enzyme Assays

Matrix Metalloproteinase family including for example MMP12, MMP13.

Recombinant human MMP12 catalytic domain may be expressed and purified as described by Parkar A.A. *et al*, (2000), Protein Expression and Purification, 20:152. The purified enzyme can be used to monitor inhibitors of activity as follows: MMP12 (50 ng/ml final concentration) is incubated for 30 minutes at RT in assay buffer (0.1M Tris-HCl, pH 7.3 containing 0.1M NaCl, 20mM $CaCl_2$, 0.040 mM ZnCl and 0.05% (w/v) Brij 35) using the synthetic substrate Mac-Pro-Cha-Gly-Nva-His-Ala-Dpa-NH2 in the presence or absence of inhibitors. Activity is determined by measuring the fluorescence at λex 328nm and λem 393nm. Percent inhibition is calculated as follows: % Inhibition is equal to the [$Fluorescence_{plus\ inhibitor}$ - $Fluorescence_{background}$] divided by the [$Fluorescence_{minus\ inhibitor}$ - $Fluorescence_{background}$].

Recombinant human proMMP13 may be expressed and purified as described by Knauper *et al.* [V. Knauper *et al.*, (1996) The Biochemical Journal 271:1544-1550 (1996)]. The purified enzyme can be used to monitor inhibitors of activity as follows: purified proMMP13 is activated using 1mM amino phenyl mercuric acid (APMA), 20 hours at 21°C; the activated MMP13 (11.25ng per assay) is incubated for 4-5 hours at 35°C in assay buffer (0.1M Tris-HCl, pH 7.5 containing 0.1M NaCl, 20mM CaCl2, 0.02 mM ZnCl and 0.05% (w/v) Brij 35) using the synthetic substrate 7-methoxycoumarin-4-yl)acetyl.Pro.Leu.Gly.Leu.N-3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl.Ala.Arg.NH_2 in the presence or absence of inhibitors. Activity is determined by measuring the fluorescence at λex 328nm and λem 393nm. Percent inhibition is calculated as follows: % Inhibition is equal to the [$Fluorescence_{plus\ inhibitor}$ - $Fluorescence_{background}$] divided by the [$Fluorescence_{minus\ inhibitor}$ - $Fluorescence_{background}$].

A similar protocol can be used for other expressed and purified pro MMPs using substrates and buffers conditions optimal for the particular MMP, for instance as described in C. Graham Knight *et al.*, (1992) FEBS Lett. 296(3):263-266.

Adamalysin family including for example TNF convertase

The ability of the compounds to inhibit proTNFα convertase enzyme may be assessed using a partially purified, isolated enzyme assay, the enzyme being obtained from the membranes of THP-1 as described by K. M. Mohler *et al.*, (1994) Nature 370:218-220. The purified enzyme activity and inhibition thereof is determined by incubating the partially purified enzyme in the presence or absence of test compounds using the substrate 4',5'-Dimethoxy-fluoresceinyl Ser.Pro.Leu.Ala.Gln.Ala.Val.Arg.Ser.Ser.Ser.Arg.Cys(4-(3-succinimid-1-yl)-fluorescein)-NH_2 in assay buffer (50mM Tris HCl, pH 7.4 containing 0.1% (w/v) Triton X-100 and 2mM $CaCl_2$), at 26°C for 18 hours. The amount of inhibition is determined as for MMP13 except λex 490nm and λem 530nm were used. The substrate was synthesised as follows. The peptidic part of the substrate was assembled on Fmoc-NH-Rink-MBHA-polystyrene resin either manually or on an automated peptide synthesiser by standard methods involving the use of Fmoc-amino acids and O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) as coupling agent with at least a 4- or 5-fold excess of Fmoc-amino acid and HBTU. Ser^1 and Pro^2 were double-coupled. The following side chain protection strategy was employed; Ser^1(But), Gln^5(Trityl), $Arg^{8,12}$(Pmc or Pbf), $Ser^{9,10,11}$(Trityl), Cys^{13}(Trityl). Following assembly, the N-terminal Fmoc-protecting group was removed by treating the Fmoc-peptidyl-resin with in DMF. The amino-peptidyl-resin so obtained was acylated by treatment for 1.5-2hr at 70°C with 1.5-2 equivalents of 4',5'-dimethoxy-fluorescein-4(5)-carboxylic acid [Khanna & Ullman, (1980) Anal Biochem. 108:156-161) which had been preactivated with diisopropylcarbodiimide and 1-hydroxybenzotriazole in DMF]. The dimethoxyfluoresceinyl-peptide was then simultaneously deprotected and cleaved from the resin by treatment with trifluoroacetic acid containing 5% each of water and triethylsilane. The dimethoxyfluoresceinyl-peptide was isolated by evaporation, trituration with diethyl ether and filtration. The isolated peptide was reacted with 4-(N-maleimido)-fluorescein in

DMF containing diisopropylethylamine, the product purified by RP-HPLC and finally isolated by freeze-drying from aqueous acetic acid. The product was characterised by MALDI-TOF MS and amino acid analysis.

Natural Substrates

The activity of the compounds of the invention as inhibitors of aggrecan degradation may be assayed using methods for example based on the disclosures of E. C. Arner *et al.*, (1998) Osteoarthritis and Cartilage 6:214-228; (1999) Journal of Biological Chemistry, 274 (10), 6594-6601 and the antibodies described therein. The potency of compounds to act as inhibitors against collagenases can be determined as described by T. Cawston and A. Barrett (1979) Anal. Biochem. 99:340-345.

Inhibition of metalloproteinase activity in cell/tissue based activity

Test as an agent to inhibit membrane sheddases such as TNF convertase

The ability of the compounds of this invention to inhibit the cellular processing of TNFα production may be assessed in THP-1 cells using an ELISA to detect released TNF essentially as described K. M. Mohler *et al.*, (1994) Nature 370:218-220. In a similar fashion the processing or shedding of other membrane molecules such as those described in N. M. Hooper *et al.*, (1997) Biochem. J. 321:265-279 may be tested using appropriate cell lines and with suitable antibodies to detect the shed protein.

Test as an agent to inhibit cell based invasion

The ability of the compound of this invention to inhibit the migration of cells in an invasion assay may be determined as described in A. Albini *et al.*, (1987) Cancer Research 47:3239-3245.

Test as an agent to inhibit whole blood TNF sheddase activity

The ability of the compounds of this invention to inhibit TNFα production is assessed in a human whole blood assay where LPS is used to stimulate the release of TNFα. Heparinized (10Units/ml) human blood obtained from volunteers is diluted 1:5 with medium (RPMI1640 + bicarbonate, penicillin, streptomycin and glutamine) and incubated (160μl) with 20μl of test compound (triplicates), in DMSO or appropriate vehicle, for 30 min at 37°C in a humidified (5%CO_2/95%air) incubator, prior to addition of 20μl LPS (E. coli. 0111:B4; final concentration 10μg/ml). Each assay includes controls of diluted blood incubated with medium alone (6 wells/plate) or a known TNFα inhibitor as standard. The plates are then incubated for 6 hours at 37°C (humidified incubator), centrifuged (2000rpm for 10 min; 4°C), plasma harvested (50-100μl) and stored in 96 well plates at -70°C before subsequent analysis for TNFα concentration by ELISA.

Test as an agent to inhibit in vitro cartilage degradation

The ability of the compounds of this invention to inhibit the degradation of the aggrecan or collagen components of cartilage can be assessed essentially as described by K. M. Bottomley *et al.*, (1997) Biochem J. 323:483-488.

Pharmacodynamic test

To evaluate the clearance properties and bioavailability of the compounds of this invention an ex vivo pharmacodynamic test is employed which utilises the synthetic substrate assays above or alternatively HPLC or Mass spectrometric analysis. This is a generic test which can be used to estimate the clearance rate of compounds across a range

of species. Animals (e,g. rats, marmosets) are dosed iv or po with a soluble formulation of compound (such as 20% w/v DMSO, 60% w/v PEG400) and at subsequent time points (e.g. 5, 15, 30, 60, 120, 240, 480, 720, 1220 mins) the blood samples are taken from an appropriate vessel into 10U heparin. Plasma fractions are obtained following centrifugation and the plasma proteins precipitated with acetonitrile (80% w/v final concentration). After 30 mins at -20°C the plasma proteins are sedimented by centrifugation and the supernatant fraction is evaporated to dryness using a Savant speed vac. The sediment is reconstituted in assay buffer and subsequently analysed for compound content using the synthetic substrate assay. Briefly, a compound concentration-response curve is constructed for the compound undergoing evaluation. Serial dilutions of the reconstituted plasma extracts are assessed for activity and the amount of compound present in the original plasma sample is calculated using the concentration-response curve taking into account the total plasma dilution factor.

In vivo assessment

Test as an anti-TNF agent

The ability of the compounds of this invention as *ex vivo* TNFα inhibitors is assessed in the rat. Briefly, groups of male Wistar Alderley Park (AP) rats (180-210g) are dosed with compound (6 rats) or drug vehicle (10 rats) by the appropriate route e.g. peroral (p.o.), intraperitoneal (i.p.), subcutaneous (s.c.). Ninety minutes later rats are sacrificed using a rising concentration of CO_2 and bled out via the posterior vena cavae into 5 Units of sodium heparin/ml blood. Blood samples are immediately placed on ice and centrifuged at 2000 rpm for 10 min at 4°C and the harvested plasmas frozen at -20°C for subsequent assay of their effect on TNFα production by LPS-stimulated human blood. The rat plasma samples are thawed and 175µl of each sample are added to a set format pattern in a 96U well plate. Fifty µl of heparinized human blood is then added to each well, mixed and the plate is incubated for 30 min at 37°C (humidified incubator). LPS (25µl; final concentration 10µg/ml) is added to the wells and incubation continued for a further 5.5 hours. Control wells are incubated with 25µl of medium alone. Plates are then centrifuged

for 10 min at 2000 rpm and 200µl of the supernatants are transferred to a 96 well plate and frozen at -20°C for subsequent analysis of TNF concentration by ELISA.

Data analysis by dedicated software calculates for each compound/dose:

Percent inhibition of TNFα= $\frac{\text{Mean TNFα (Controls)} - \text{Mean TNFα (Treated)} \times 100}{\text{Mean TNFα (Controls)}}$

Test as an anti-arthritic agent

Activity of a compound as an anti-arthritic is tested in the collagen-induced arthritis (CIA) as defined by D. E. Trentham *et al.*, (1977) J. Exp. Med. 146,:857. In this model acid soluble native type II collagen causes polyarthritis in rats when administered in Freunds incomplete adjuvant. Similar conditions can be used to induce arthritis in mice and primates.

Test as an anti-cancer agent

Activity of a compound as an anti-cancer agent may be assessed essentially as described in I. J. Fidler (1978) Methods in Cancer Research 15:399-439, using for example the B16 cell line (described in B. Hibner *et al.*, Abstract 283 p75 10th NCI-EORTC Symposium, Amsterdam June 16 – 19 1998).

Test as an anti-emphysema agent

Activity of a compound as an anti-emphysema agent may be assessed essentially as described in Hautamaki *et al* (1997) Science, 277: 2002.

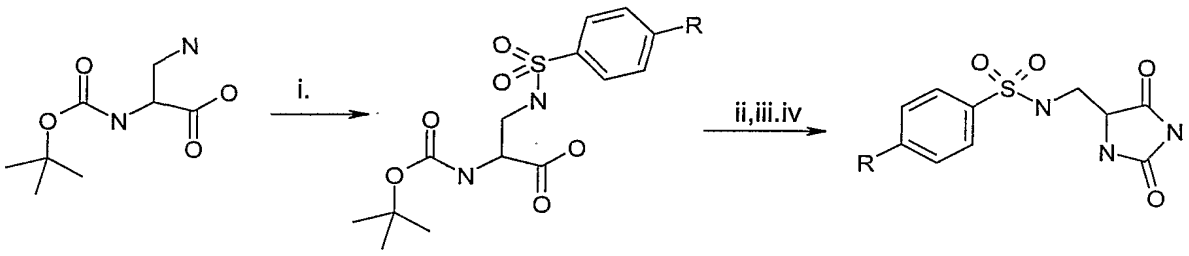
The invention will now be illustrated but not limited by the following Examples:

General analytical methods: ^{1}H-NMR spectra were recorded on either a Varian ^{Unity}*Inova* 400MHz or Varian *Mercury-VX* 300MHz instrument. The central solvent peak of chloroform-*d* (δ_H 7.27 ppm), dimethylsulfoxide-d_6 (δ_H 2.50 ppm) or methanol-d_4 (δ_H 3.31 ppm) were used as internal references. Low resolution mass spectra were obtained on a Agilent 1100 LC-MS system equipped with an APCI ionization chamber.

EXAMPLE 1

***N*-{[(4*S*)-2,5-dioxoimidazolidinyl]methyl}-4-(4- fluorophenoxy) benzenesulfonamide and**

***N*-{[(4*S*)-2,5-dioxoimidazolidinyl]methyl}[1,1'-biphenyl]-4-sulfonamide**



i $C_6H_4SO_2Cl$ ii HCl/dioxane iii KCNO iv wt. HCl, 100°C

R = 4-fluorophenoxy or R = phenyl

To the stirred solution of N-alfa-BOC-(S)-diaminopropionic acid (100 mg,0.5 mmol) in 2.5 ml water containing 0.04g (0.55 mmol) of sodium carbonate was added the soln.of the sulfonyl chloride (0.5 mmol) in 2.5 ml of dioxane.The solution was stirred overnight at room temperature, distributed between ethyl acetate (10 ml) and ca 20% citric acid (10 ml),the water phase was three times reextracted with ethyl acetate,organic extract was washed with brine,dried,evaporated and the residue was treated with 4N HCl in dioxane.The mixture was stirred for 20 min,evaporated and dried in vacuo for 4 hrs at 40 C.Then,the residue was quenched with 3ml of water solution of sodium carbonate (0.08g,

0.85 mmol) and 0.9 g (1.1 mmol) of potassium cyanate was added and the mixture was stirred for 4 hrs at 100 C.After this period,1 ml of conc.HCl as added,stirred for 1 hr at the same temperature and then allowed to stand at room temperature overnight.The crystalls were filtered,washed with dist.water and dried in vacuo (recrystallised from wt.ethanol if necessary)

***N*-{[(4*S*)-2,5-dioxoimidazolidinyl]methyl}-4-(4- fluorophenoxy) benzenesulfonamide**

MS:m/z=380.1

***N*-{[(4*S*)-2,5-dioxoimidazolidinyl]methyl}[1,1'-biphenyl]-4-sulfonamide**

MS:m/z=346.1

1H NMR:(DMSO):3.00 m (1.5H),3.10m(0.6H),(**CH_2**), 4.10 m (1H,**CH**),7.5 m (3H),7.70d (2H),7.4 s (4H).

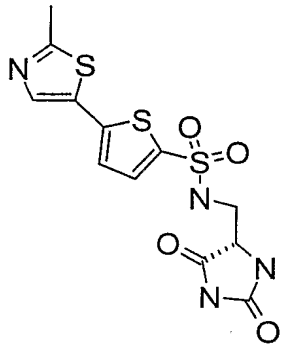
EXAMPLE 2

Compounds of formula II were prepared wherein Y1 is O, Y2 is O, X is NR1, R1 is H, R2 is H, m is 1, R3 is H, R4 is H, Z is $SO_2N(R6)$, R6 is H, (C1-4)alkyl, methylbenzyl, or methylpyridyl, A is a direct bond, and R5 varies.

The syntheses were performed in parallel on 20-well plate manually operated. The amino acid (20 um) was dissolved in 5 ml water containing 6.36 mg (60 um) of sodium carbonate. 0.5 ml of the solution was pipetted to each well, followed by 0.5 ml of dioxane solution containing 20 um of corresponding sulfonyl chloride. The reaction mixture was shaken for 18 hrs at room temperature, diluted with 2 ml of methanol and treated with 20 mg of Lewatite S100 in each well (acid form) for 5 min. Then all reaction mixtures was filtered, evaporated in vacuo and the evaporate was treated with 1 ml of 4 N HCl in dioxane for 30 min, evaporated in vacuo and 0.5 ml of 0.5 M wt. solution of potassium cyanate was added and heated to 100°C for 3 hrs. Then 10 mg of Lewatite S100 (acid form) was added to each well after being cooled to room temperature, followed by 2 ml of methanol, evaporated in vacuo and threated with trifluoroacetic acid at 80°C for 2 hrs. After being evaporated, the residue was purified by flash chromatography on silica

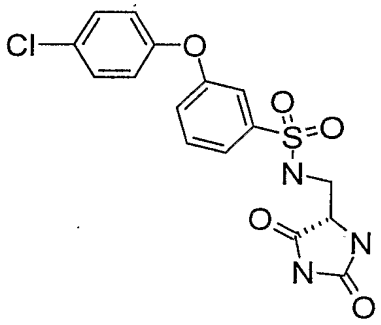
using ethyl acetate-methanol gradient (up to 10% MeOH). The purity and mol.weight was monitored by HPLC-MS. Yields : 0.5-1 mg per each well.

5-(2-Methyl-thiazol-5-yl)-thiophene-2-sulfonic acid (2,5-dioxo-imidazolidin-4-ylmethyl)-amide



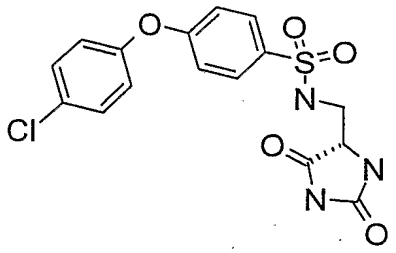
LC-MS (APCI) $M^+ + H^+ = 373.4$ (m/z)

3-(4-Chloro-phenoxy)*N*-(2,5-dioxo-imidazolidin-4-ylmethyl)-benzenesulfonamide



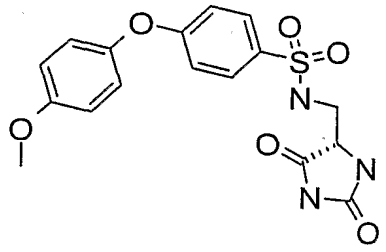
LC-MS (APCI) $M^+ + H^+ = 396.8$(m/z)

4-(4-Chloro-phenoxy)*N*-(2,5-dioxo-imidazolidin-4-ylmethyl)-benzenesulfonamide



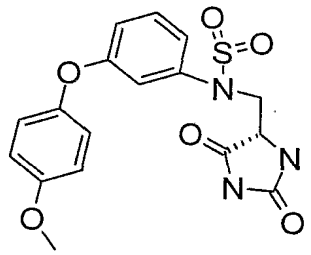
LC-MS (APCI) $M^+ + H^+ = 396.8$(m/z)

***N*-(2,5-Dioxo-imidazolidin-4-ylmethyl)-4-(4-methoxy-phenoxy)-benzenesulfonamide**



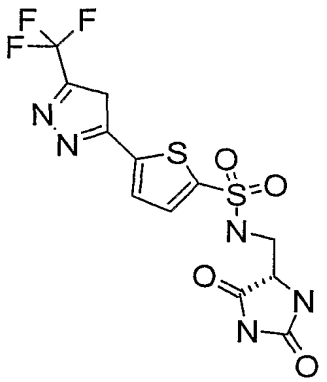
LC-MS (APCI) $M^+ + H^+ = 392.6$(m/z)

***N*-(2,5-Dioxo-imidazolidin-4-ylmethyl)-3-(4-methoxy-phenoxy)-benzenesulfonamide**



LC-MS (APCI) $M^+ + H^+ = 392.6$(m/z)

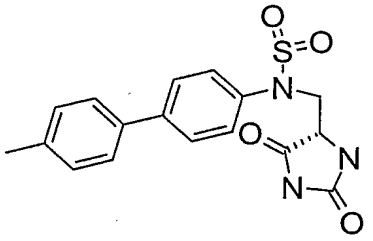
5-(5-Trifluoromethy*H*-pyrazol-3-yl)-thiophene-2-sulfonic acid (2,5-dioxo-imidazolidin-4-ylmethyl)-amide



LC-MS (APCI) $M^+ + H^+ = 410.4$(m/z)

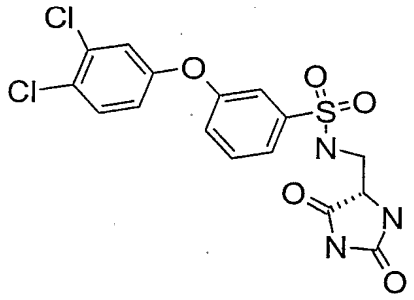
***N*-(2,5-Dioxo-imidazolidin-4-ylmethyp -4-**

-tolyloxy-benzenesulfonamide



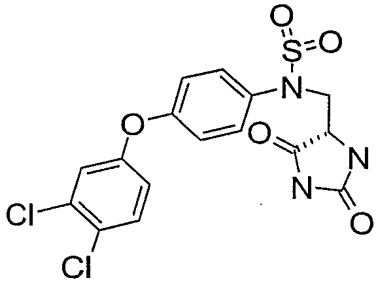
LC-MS (APCI) $M^+ + H^+ = 376.4$(m/z)

3-(3,4-Dichloro-phenoxy)- *N* -(dioxo-imidazolidin-4-ylmethyl)-benzenesulfonamide



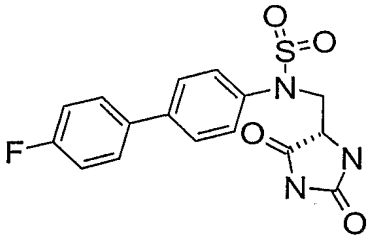
LC-MS (APCI) $M^+ + H^+ = 430.6$(m/z)

4-(3,4-Dichloro-phenoxy)- *N* -(2,5-dioxo-imidazolidin-4-ylmethyl)-benzenesulfonamide



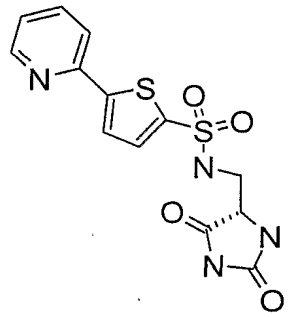
LC-MS (APCI) $M^+ + H^+ = 430.6$(m/z)

4'-Fluoro-biphenyl-4-sulfonic acid (2,5-dioxo-imidazolidin-4-ylmethyl)-amide



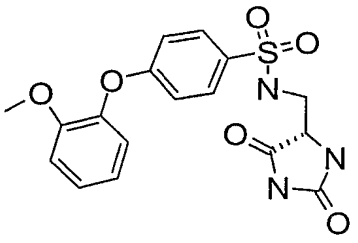
LC-MS (APCI) $M^+ + H^+ = 364.4$(m/z)

5-Pyridin-2-yl-thiophene-2-sulfonic acid (2,5-dioxo-imidazolidin-4-ylmethyl)-amide



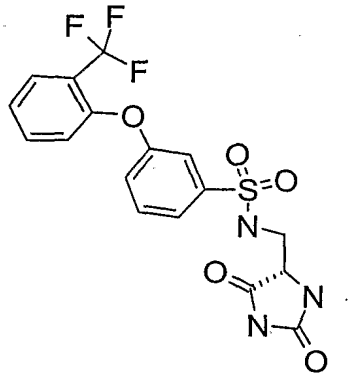
LC-MS (APCI) $M^+ + H^+ = 353.4$(m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-4-(2-methoxy-phenoxy)-benzenesulfonamide



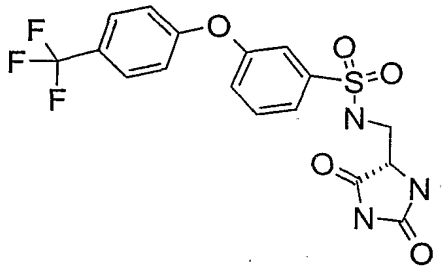
LC-MS (APCI) $M^+ + H^+ = 392.5$(m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-3-(2-trifluoromethyl-phenoxy)-benzenesulfonamide



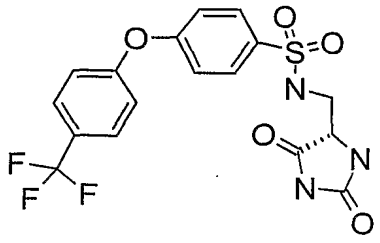
LC-MS (APCI) $M^+ + H^+ = 430.4$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-3-(4-trifluoromethyl-phenoxy)-benzenesulfonamide



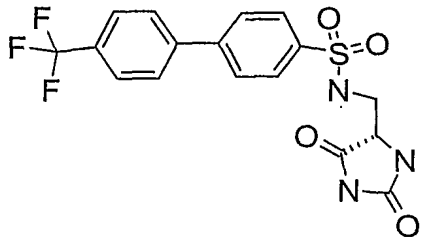
LC-MS (APCI) $M^+ + H^+ = 430.4$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-4-(4-trifluoromethyl-phenoxy)-benzenesulfonamide



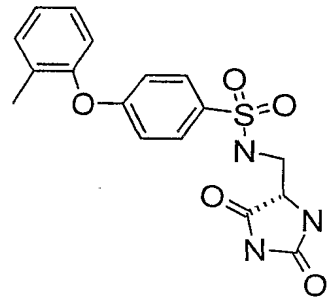
LC-MS (APCI) $M^+ + H^+ = 430.4$ (m/z)

4'-Trifluoromethyl-biphenyl-4-sulfonic acid (2,5-dioxo-imidazolidin-4-ylmethyl)-amide



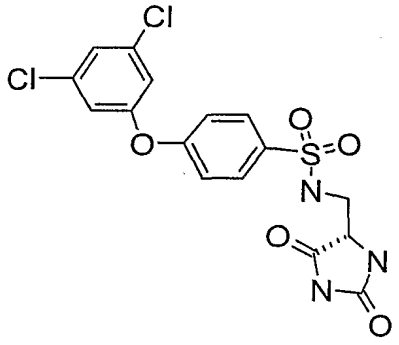
LC-MS (APCI) $M^+ + H^+ = 414.4$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-4-*o*-tolyloxy-benzenesulfonamide



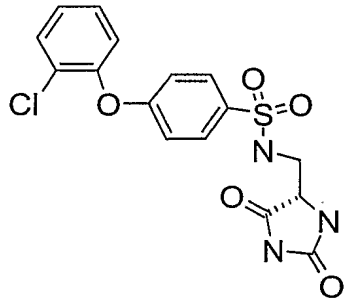
LC-MS (APCI) $M^+ + H^+ = 376.4$ (m/z)

4-(3,5-Dichloro-phenoxy)-*N*-(2,5-dioxo-imidazolidin-4-ylmethyl)-benzenesulfonamide



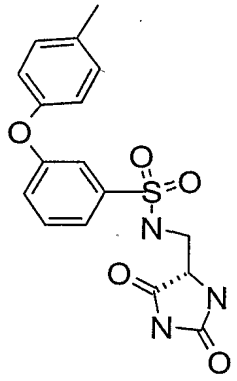
LC-MS (APCI) $M^+ + H^+ = 431.3$ (m/z)

4-(2-Chloro-phenoxy)-*N*-(2,5-dioxo-imidazolidin-4-ylmethyl)-benzenesulfonamide



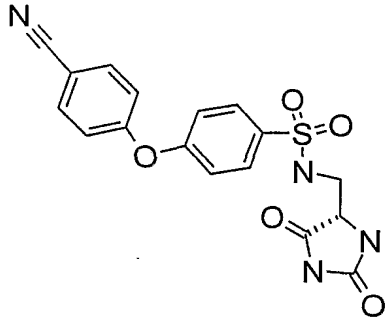
LC-MS (APCI) $M^+ + H^+ = 396.8$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-3-*p*-tolyloxy-benzenesulfonamide



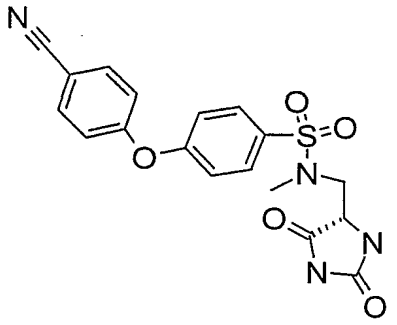
LC-MS (APCI) $M^+ + H^+ = 376.4$ (m/z)

4-(4-Cyano-phenoxy)-*N*-(2,5-dioxo-imidazolidin-4-ylmethyl)-benzenesulfonamide



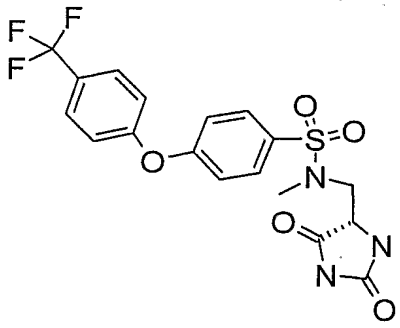
LC-MS (APCI) $M^+ + H^+ = 387.4$ (m/z)

4-(4-Cyano-phenoxy)-*N*-(2,5-dioxo-imidazolidin-4-ylmethyl)-*N*-methyl-benzenesulfonamide



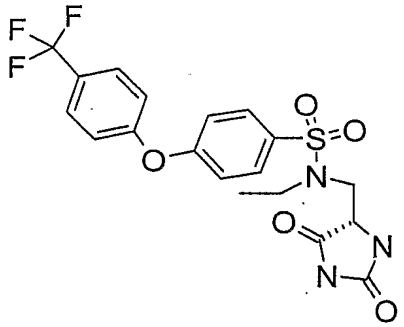
LC-MS (APCI) $M^+ + H^+ = 401.4$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-*N*-methyl-4-(4-trifluoromethyl-phenoxy)-benzenesulfonamide



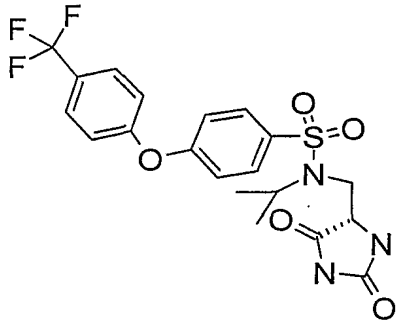
LC-MS (APCI) $M^+ + H^+ = 444.4$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-*N*-ethyl-4-(4-trifluoromethyl-phenoxy)-benzenesulfonamide



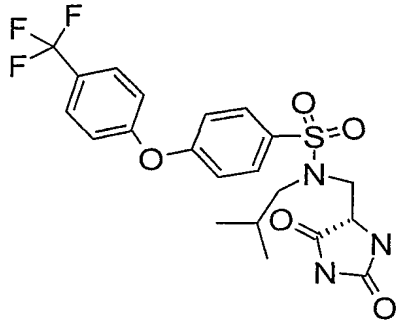
LC-MS (APCI) $M^+ + H^+ = 458.4$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-*N*-isopropyl-4-(4-trifluoromethyl-phenoxy)-benzenesulfonamide



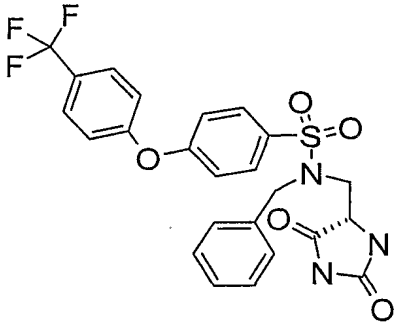
LC-MS (APCI) $M^+ + H^+ = 472.4$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-*N*-isobutyl-4-(4-trifluoromethyl-phenoxy)-benzenesulfonamid



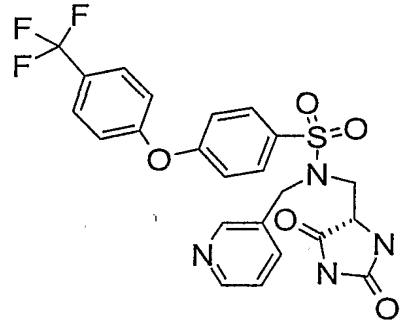
LC-MS (APCI) $M^+ + H^+ = 486.5$ (m/z)

N-Benzyl-*N*-(2,5-dioxo-imidazolidin-4-ylmethyl)-4-(4-trifluoromethyl-phenoxy)-benzenesulfonamide



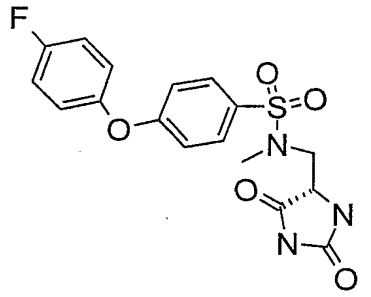
LC-MS (APCI) $M^+ + H^+ = 520.5$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-*N*-pyridin-3-ylmethyl-4-(4-trifluoromethyl-phenoxy)-benzene



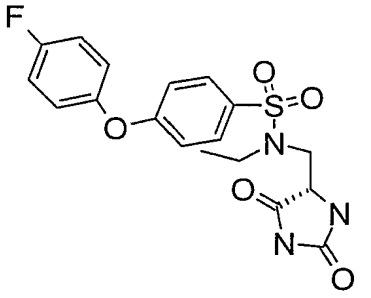
LC-MS (APCI) $M^+ + H^+ = 521.5$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-4-(4-fluoro-phenoxy)-*N*-methyl-benzenesulfonamide



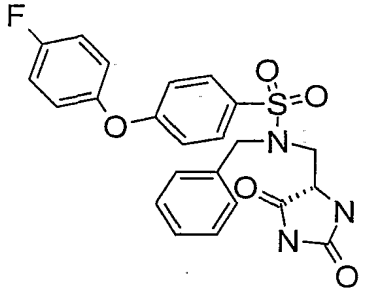
LC-MS (APCI) $M^+ + H^+ = 394.4$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-*N*-ethyl-4-(4-fluoro-phenoxy)-benzenesulfonamide



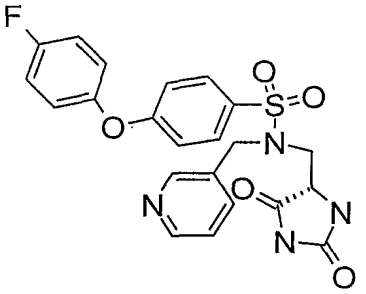
LC-MS (APCI) $M^+ + H^+ = 408.4$ (m/z)

N-Benzyl-*N*-(2,5-dioxo-imidazolidin-4-ylmethyl)-4-(4-fluoro-phenoxy)-benzenesulfonamide



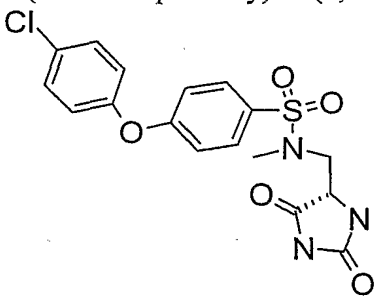
LC-MS (APCI) $M^+ + H^+ = 470.5$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-4-(4-fluoro-phenoxy)-*N*-pyridin-3-ylmethyl-benzenesulfonami



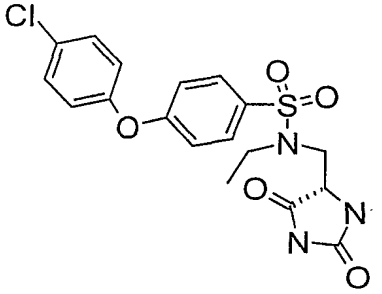
LC-MS (APCI) $M^+ + H^+ = 471.5$ (m/z)

4-(4-Chloro-phenoxy)-*N*-(2,5-dioxo-imidazolidin-4-ylmethyl)-*N*-methyl-benzenesulfonamide



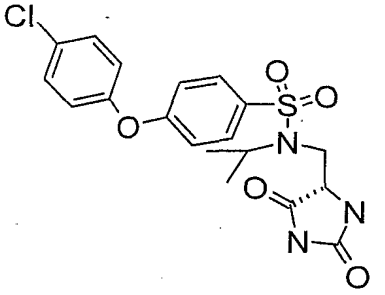
LC-MS (APCI) $M^+ + H^+ = 410.5$ (m/z)

4-(4-Chloro-phenoxy)-*N*-(2,5-dioxo-imidazolidin-4-ylmethyl)-*N*-ethyl-benzenesulfonamide



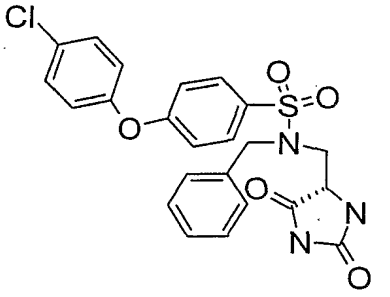
LC-MS (APCI) $M^+ + H^+ = 424.88$ (m/z)

4-(4-Chloro-phenoxy)-*N*-(2,5-dioxo-imidazolidin-4-ylmethyl)-*N*-isopropyl-benzenesulfonamide



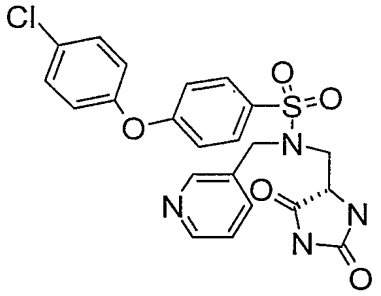
LC-MS (APCI) $M^+ + H^+ = 424.88$ (m/z)

N-Benzyl-4-(4-chloro-phenoxy)-*N*-(2,5-dioxo-imidazolidin-4-ylmethyl)-benzenesulfonamide



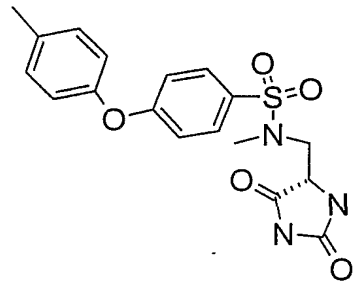
LC-MS (APCI) $M^+ + H^+ = 486.9$ (m/z)

4-(4-Chloro-phenoxy)-*N*-(2,5-dioxo-imidazolidin-4-ylmethyl)-*N*-pyridin-3-ylmethyl-benzenesulfonamide



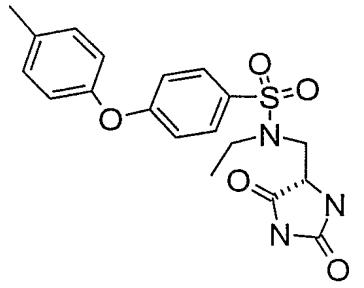
LC-MS (APCI) $M^+ + H^+ = 487.9$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-*N*-methyl-4-*p*-tolyloxy-benzenesulfonamide



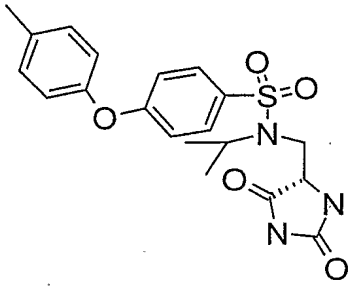
LC-MS (APCI) $M^+ + H^+ = 390.4$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-*N*-ethyl-4-*p*-tolyloxy-benzenesulfonamide



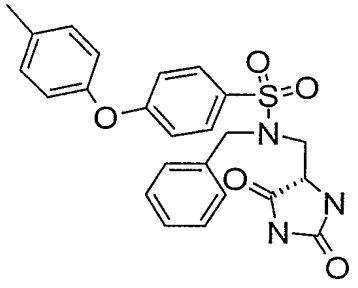
LC-MS (APCI) $M^+ + H^+ = 404.5$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-*N*-isopropyl-4-*p*-tolyloxy-benzenesulfonamide



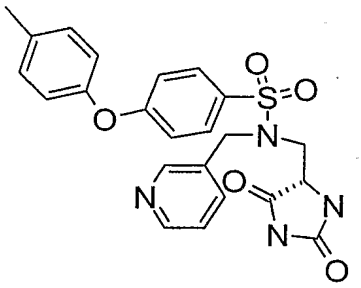
LC-MS (APCI) $M^+ + H^+ = 418.5$ (m/z)

N-Benzyl-*N*-(2,5-dioxo-imidazolidin-4-ylmethyl)-4-*p*-tolyloxy-benzenesulfonamide



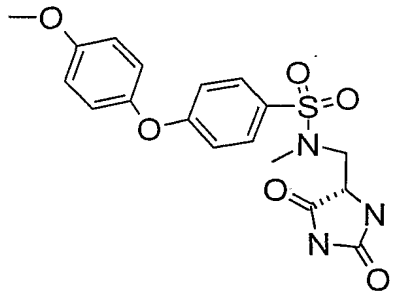
LC-MS (APCI) $M^+ + H^+ = 466.5$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-*N*-pyridin-3-ylmethyl-4-*p*-tolyloxy-benzenesulfonamide



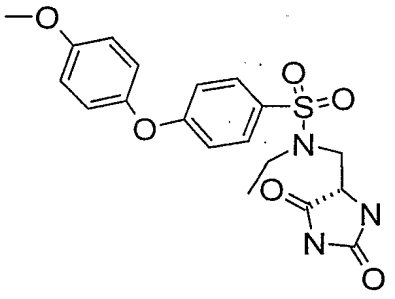
LC-MS (APCI) $M^+ + H^+ = 467.5$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-4-(4-methoxy-phenoxy)-*N*-methyl-benzenesulfonamide



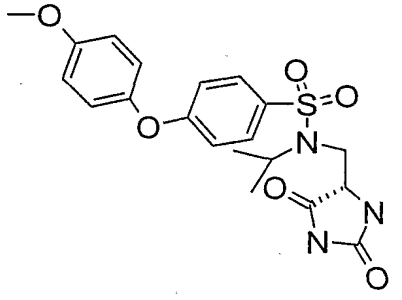
LC-MS (APCI) $M^+ + H^+ = 406.5$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-*N*-ethyl-4-(4-methoxy-phenoxy)-benzenesulfonamide



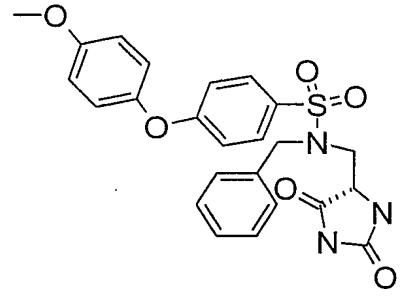
LC-MS (APCI) $M^+ + H^+ = 420.5$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-*N*-isopropyl-4-(4-methoxy-phenoxy)-benzenesulfonamide



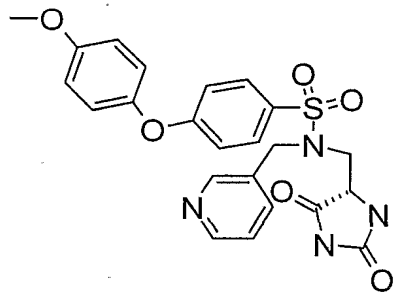
LC-MS (APCI) $M^+ + H^+ = 433.5$ (m/z)

N-Benzyl-*N*-(2,5-dioxo-imidazolidin-4-ylmethyl)-4-(4-methoxy-phenoxy)-benzenesulfonamide



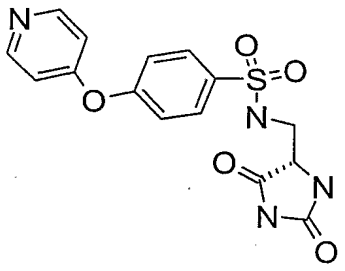
LC-MS (APCI) $M^+ + H^+ = 482.5$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-4-(4-methoxy-phenoxy)-*N*-pyridin-3-ylmethyl-benzenesulfonam



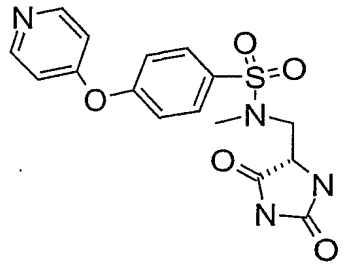
LC-MS (APCI) $M^+ + H^+ = 483.5$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-4-(pyridin-4-yloxy)-benzenesulfonamide



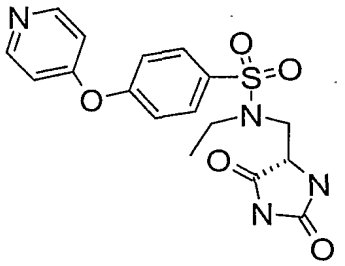
LC-MS (APCI) $M^+ + H^+ = 363.5$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-*N*-methyl-4-(pyridin-4-yloxy)-benzenesulfonamide



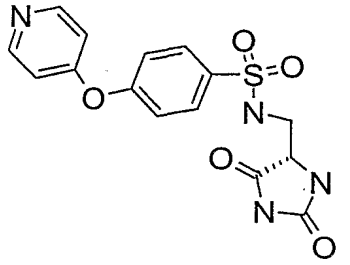
LC-MS (APCI) $M^+ + H^+ = 377.4$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-*N*-ethyl-4-(pyridin-4-yloxy)-benzenesulfonamide



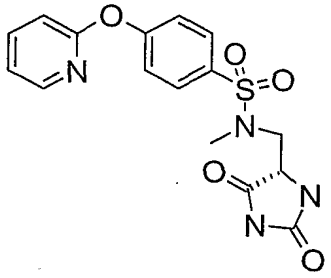
LC-MS (APCI) $M^+ + H^+ = 363.4$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-4-(pyridin-4-yloxy)-benzenesulfonamide



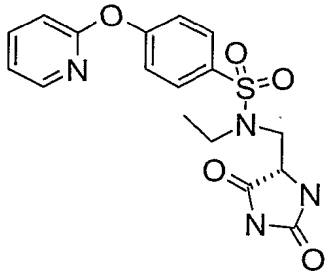
LC-MS (APCI) $M^+ + H^+ = 363.5$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-4-(pyridin-2-yloxy)-benzenesulfonamide



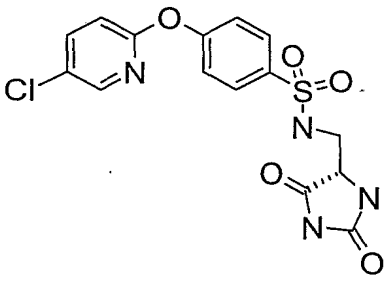
LC-MS (APCI) $M^+ + H^+ = 376.4$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-*N*-ethyl-4-(pyridin-2-yloxy)-benzenesulfonamide



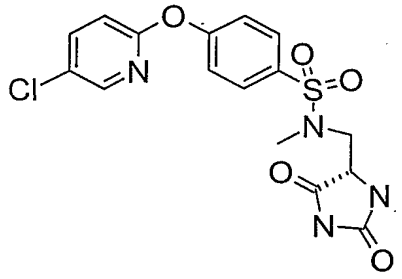
LC-MS (APCI) $M^+ + H^+ = 391.4$ (m/z)

4-(5-Chloro-pyridin-2-yloxy)-*N*-(2,5-dioxo-imidazolidin-4-ylmethyl)-benzenesulfonamide



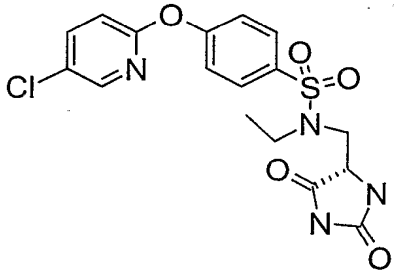
LC-MS (APCI) $M^+ + H^+ = 397.8$ (m/z)

4-(5-Chloro-pyridin-2-yloxy)-*N*-(2,5-dioxo-imidazolidin-4-ylmethyl)-*N*-methyl-benzenesulfonamide



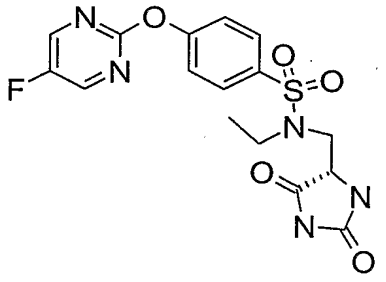
LC-MS (APCI) $M^+ + H^+ = 410.8$ (m/z)

4-(5-Chloro-pyridin-2-yloxy)-*N*-(2,5-dioxo-imidazolidin-4-ylmethyl)-*N*-ethyl-benzenesulfonamide



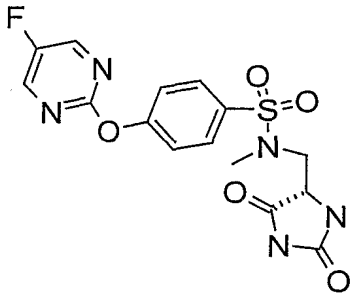
LC-MS (APCI) $M^+ + H^+ = 425.8$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-*N*-ethyl-4-(5-fluoro-pyrimidin-2-yloxy)-benzenesulfonamide



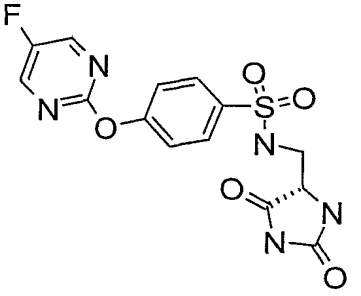
LC-MS (APCI) $M^+ + H^+ = 409.8$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-4-(5-fluoro-pyrimidin-2-yloxy)-*N*-methyl-benzenesulfonamide



LC-MS (APCI) $M^+ + H^+ = 396.4$ (m/z)

N-(2,5-Dioxo-imidazolidin-4-ylmethyl)-4-(5-fluoro-pyrimidin-2-yloxy)-benzenesulfonamide



LC-MS (APCI) $M^+ + H^+ = 382.4$ (m/z)

EXAMPLE 3

Compounds were prepared according to Scheme 2 as shown in the description above for compounds of formula II.

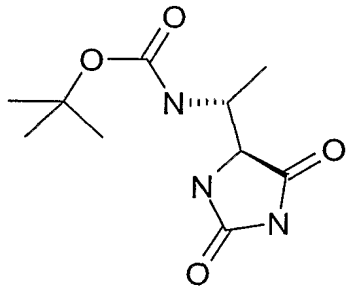
(a) **Preparation of starting materials (aldehydes or ketones)**

Aldehydes were prepared according to the procedure described by *Fehrentz JA and Castro B,* Synthesis, 676, (1983). Ketones were prepared according to the procedure described by *Nahm S and Weinreb SM :*Tetrahedron Lett.**22,** 3815, (1981).

(b) **Preparation of intermediate hydantoins**

The aldehyde or ketone (5 mmol) was dissolved in 50% water ethanol (10 ml) and 0.55 g (10 mmol) of sodium cyanide and 2.7 g (25 mmol) of ammonium carbonate was added and the mixture was heated in the sealed tube to 80°C for 6 hrs. Then it was cooled, pH was adjusted to 4 and it was evaporated in vacuo. The residue was distributed between water (10 ml) and ethyl acetate and water phase was 3-times re-extracted with ethyl acetate, then evaporated and diastereoisomeres were separated by silica chromatography (grad.TBME-methanol 0-10% MeOH). The following hydantoins were prepared.

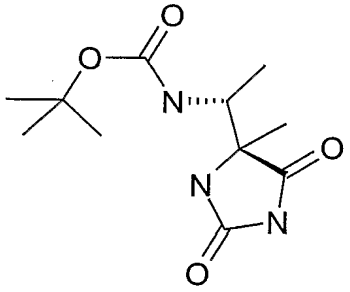
R-1-(2,5-dioxoimidazolidin-4-S-yl)-ethyl carbamic acid *tert.* butylester



LC-MS(APCI):) $M^+ + H^+ = 244.4$,) $M^+ - 56$ (isobutylene) 188.6,) M^+-BOC=144.4 (main peak)

H-NMR ($CDCl_3$ .ppm):1.23d (3H),1.45s (9.1H),4.36m(1.1H),5.30bs(1.1H),10.1bs (1.3H)

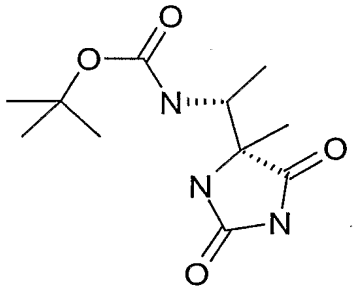
R-1-(4-Methyl-2,5dioxoimidazolin-4-S-yl)ethyl carbamoic acid



LC-MS(APCI):) $M^+ + H^+ = 258.3$,) $M^+ - 56$ (-isobutylene) 202.3,) M^+-BOC=158.3 (main peak)

H-NMR ($CDCl_3$ .ppm):1.22d (3H),1.44s (9.2H),1.58s(3.1H), 3.95m(0.9H),5.5bs (1.5H),7.9bs(0.8H)

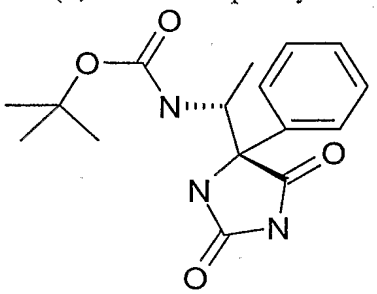
R-1-(4-Methyl-2,5dioxoimidazolin-4-R-yl)ethyl carbamoic acid *tert*-butylester



LC-MS(APCI):) $M^+ + H^+$ =258.3 ,) M^+-56 (-isobutylene) 202.3,) M^+-BOC=158.3 (main peak)

H-NMR ($CDCl_3$ .ppm):1.29d (3H),1.54s (9.1H),1.50s(2.95H),4.25m(1.1H),5.5bs (1.8H),7.9bs(0.6H)

R-1-(2,5-dioxo-4-phenylimidazolidin-4-S-yl)-ethyl carbamoic acid *tert*-butyl ester



LC-MS(APCI):) $M^+ + H^+$ =320.3) M^+-56 (-isobutylene) 264.3,) M^+-BOC=230.3 (main peak)

H-NMR ($CDCl_3$ .ppm):1.31d(3H),1.35s (9.2H),4.65m(0.9H),6.10 d (0.94H), 7.25m(3.2H),7.60d (2.05H)

tert-butyl (2S)-2-[(4R)-2,5-dioxoimidazolidin-4-yl]pyrrolidine-1-carboxylate

LC-MS: $M^+ + H^+$ =170.0 (M^+-BOC)

NMR: ($CDCl_3$ .ppm):1.26 s (9H),1.7-1.9m (3.37H),2.1-2.2m (0.84H),3.35-3,44m (1.82H),

4.1 bs (1.1H),

tert-butyl (2S)-2-[(4S)-2,5-dioxoimidazolidin-4-yl]pyrrolidine-1-carboxylate

LC-MS: $M^+ + H^+ = 170.0$ (M^+-BOC)

H-NMR: ($CDCl_3$ .ppm):1.27 s (9H),1.65-2.0 m (broad),(4.47H),3.55m(1.15H,), 3.62m (0.55H),4.4 m (0.87H),

tert-butyl (2R)-2-[(4S)-2,5-dioxoimidazolidin-4-yl]pyrrolidine-1-carboxylate

LC-MS: $M^+ + H^+ = 170.0$ (M^+-BOC)

H-NMR: ($CDCl_3$ .ppm):1.47 s (9H), 1.7-2.2m (broad) 4.30H,3.6 m (1.12H),3.8m (078H,3.6m(1.1H),

tert-butyl (2R)-2-[(4R)-2,5-dioxoimidazolidin-4-yl]pyrrolidine-1-carboxylate

LC-MS: $M^+ + H^+ = 170.0$ (M^+-BOC)

H-NMR: ($CDCl_3$ .ppm):1.47 s (9H), 1.7-2.2m (broad) 4.30H,3.6 m (1.12H),3.8m (078H,3.6m(1.1H),

tert-butyl (2R)-2-[(4S)-4-methyl-2,5-dioxoimidazolidin-4-yl]pyrrolidine-1-carboxylate

LC-MS: $M^+ + H^+ = 183.1$ (M^+-BOC)

H-NMR: ($CDCl_3$ .ppm):1.4 s (9H)1.50s(3.2H), 1.65-2.1m (broad) 4.20H,3.4 m (1.1H),3.5bs (0,78H,4.4m (0.94H),

Deprotection of BOC protected hydantoins was performed via 40% trifluoroacetic acid in DCM and the final compound 5-(1-aminoethyl) 5-alkyl imidazoline-2,4 dione trifluoracetate was precipitated by ether after evaporated to dryness.

R-5-(S-1-aminoethyl)-imidazoline-2,4-dione trifluoroacetate

LC-MS(APCI): $M^+ + H^+ = 144.2$ *(m/z)*

R-5-(1-aminoethyl)-5-S-methyl imidazolidine-2,4-dione trifluoroacetate
LC-MS(APCI): $M^+ + H^+ = 158.2$ *(m/z)*

R-5-(1-aminoethyl)-5-R-methyl imidazolidine-2,4-dione trifluoroacetate
LC-MS(APCI): $M^+ + H^+ = 158.2$ *(m/z)*

R-5-(1-aminoethyl)-5-S-phenylimidazolidine-2,4-dione trifluoroacetate
LC-MS(APCI): $M^+ + H^+ = 220.3$ *(m/z)*
(5R)-5-[(2S)-pyrrolidin-2-yl]imidazolidine-2,4-dione trifluoroacetate
LC-MS(APCI): $M^+ + H^+ = 169.1$ *(m/z)*
(5R)-5-[(2R)-pyrrolidin-2-yl]imidazolidine-2,4-dione
LC-MS(APCI): $M^+ + H^+ = 169.1$ *(m/z)*

(5R)-5-[(2S)-pyrrolidin-2-yl]imidazolidine-2,4-dione
LC-MS(APCI): $M^+ + H^+ = 169.1$ *(m/z)*

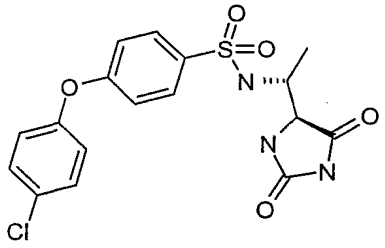
(5S)-5-[(2S)-pyrrolidin-2-yl]imidazolidine-2,4-dione
LC-MS(APCI): $M^+ + H^+ = 169.1$ *(m/z)*
(5S)-5-methyl-5-[(2R)-pyrrolidin-2-yl]imidazolidine-2,4-dione
LC-MS(APCI): $M^+ + H^+ = 183.21$ *(m/z)*

(c) **Preparation of hydantoins of formula II**

Synthesis was performed in parallel, on 20 well plates, manually operated. Each well was charged by ca 7.5 umol of the corresponding sulfonyl chloride in 0.5 ml of DCM, followed by ca 15-20 umol of the 5-(1-aminoethyl) 5-alkyl imidazoline-2,4-dione trifluoroacetate in 0.5 ml DCM (small amount of DMF added if necessary for complete dissolution) and 10 mg of the diethylaminomethyl polystyrene resin was added. The mixture was shaked overnight, filtered through 200 mg of silica gel (washed with 3-5 ml of

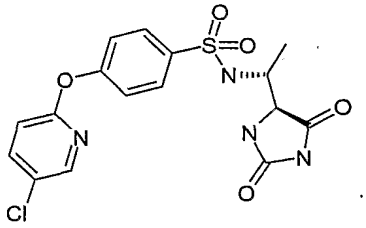
ethyl acetate and the purity was monitored by LC-MS. The solutions were evaporated to dryness to afford all expected compounds in sufficient purity.

4-R-(4-chlorophenoxy-N-(1-(2,5dioxoimidazolin-4-S-yl)-ethyl) benzenesulfonamide



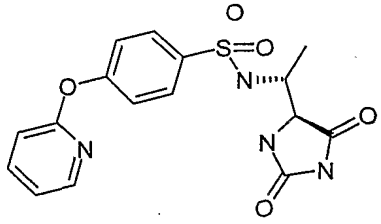
LC-MS(APCI): $M^+ + H^+ = 411.1$ *(m/z)*

4-R-(5-chloropyridin-2-oxy)-N-(1-(2,5-dioxoimidazoline-4-S-yl)-ethyl) benzenesulfonamide



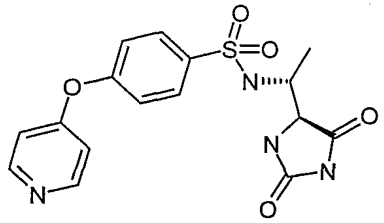
LC-MS(APCI): $M^+ + H^+ = 412.1$ *(m/z)*

R-N-(1-(2,5-dioxo-imidazolidin-S-4-yl) ethyl)-4-(pyridin-2-yloxy)-benzenesulfonamide



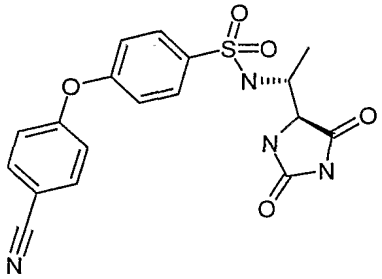
LC-MS(APCI): $M^+ + 2\ H^+ = 378.9$ *(m/z)*

R-N-(1-(2,5-dioxo-imidazolidin-S-4-yl) ethyl)-4-(pyridin-4-yloxy)-benzenesulfonamide



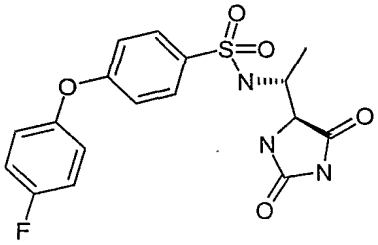
LC-MS(APCI): M^++2 H^+ =378.9 *(m/z)*

4-R-(4-cyanophenoxy-N-(1-(2,5dioxoimidazolin-4-S-yl)-ethyl) benzenesulfonamide



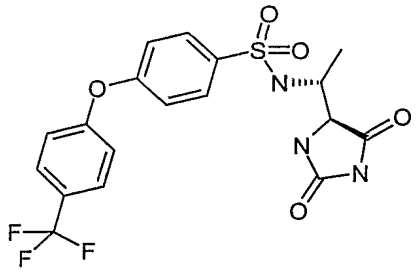
LC-MS(APCI): M^++H^+ =401.5 *(m/z)*

4-R-(4-fluorophenoxy-N-(1-(2,5dioxoimidazolin-4-S-yl)-ethyl) benzenesulfonamide



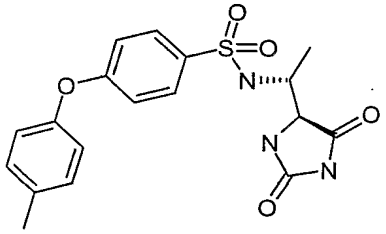
LC-MS(APCI): M^++ H^+ =394.3 *(m/z)*

4-R-(4-trifluoromethylphenoxy-N-(1-(2,5dioxoimidazolin-4-S-yl)-ethyl) benzenesulfonamide



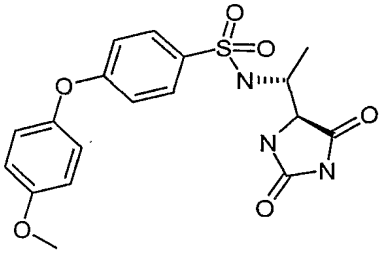
LC-MS(APCI): $M^+ + H^+ = 444.4$ *(m/z)*

4-R-(4-methylphenoxy-N-(1-(2,5dioxoimidazolin-4-S-yl)-ethyl) benzenesulfonamide



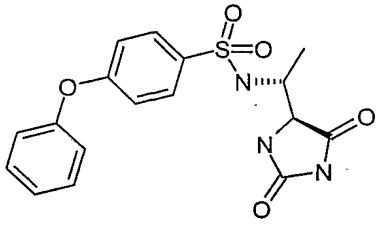
LC-MS(APCI): $M^+ + H^+ = 389.43$ *(m/z)*

4-R-(4-methoxyphenoxy-N-(1-(2,5dioxoimidazolin-4-S-yl)-ethyl) benzenesulfonamide



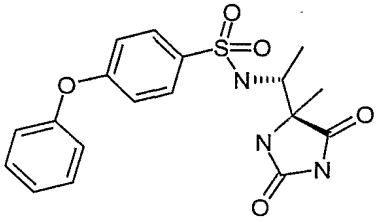
LC-MS(APCI): $M^+ + H^+ = 406.4$ *(m/z)*

4-R-(4-phenoxy-N-(1-(2,5dioxoimidazolin-4-S-yl)-ethyl) benzenesulfonamide



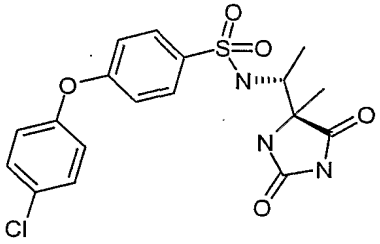
LC-MS(APCI): $M^+ + 2H^+ = 376.2$ *(m/z)*

R-N-(1-(4-methy 2,5-dioxo-imidazolidin-4-S-yl)-ethyl-4-phenoxybenzenesulfonamide



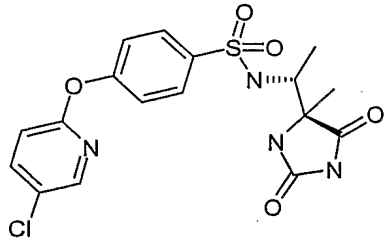
LC-MS(APCI): $M^+ + H^+ = 390.4$ *(m/z)*

4-(4-Chlorohenoxy-N-(1-(4-S-methyl-2,5-dioxoimidazolidin-4-R-yl)-ethyl benzenesulfonamide



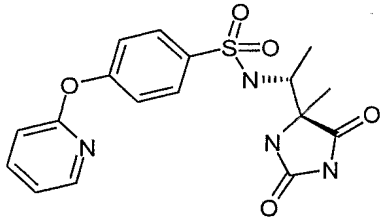
LC-MS(APCI): $M^+ + H^+ = 423.4$ *(m/z)*

4-(5-chloropyridyl-2-oxy)-N-(1-(4-S-methyl-2,5-dioxoimidazolidin-4-R-yl)-ethyl benzenesulfonamide



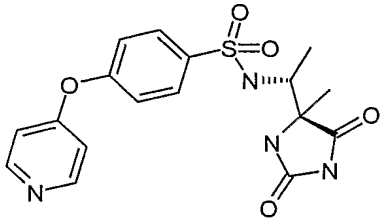
LC-MS(APCI): $M^+ + H^+ = 424.4$ *(m/z)*

N-(1-(4-S-methyl-2,5-dioxoimidazolidin-4-R-yl)-ethyl)-4-(pyridin-2-yloxy) benzenesulfonamide



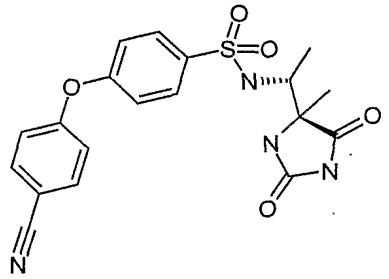
LC-MS(APCI): $M^+ + 2H^+ = 392.4$ *(m/z)*

N-(1-(4-S-methyl-2,5-dioxoimidazolidin-4-R-yl)-ethyl)-4-(pyridin-2-yloxy) benzenesulfonamide



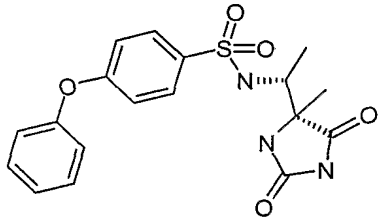
LC-MS(APCI): $M^+ + 2H^+ = 392.4$ *(m/z)*

4-(4-cyanophenoxy-N-(1-(4-S-methyl-2,5-dioxoimidazolidin-4-R-yl)-ethyl benzenesulfonamide



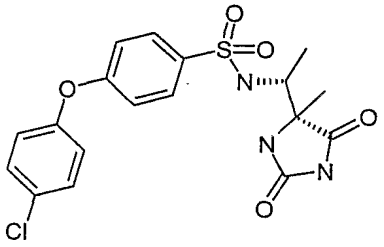
LC-MS(APCI): $M^+ + 2H^+ = 415.4$ *(m/z)*

R-N-(1-(4-methy 2,5-dioxo-imidazolidin-4-R-yl)-ethyl-4-phenoxybenzenesulfonamide



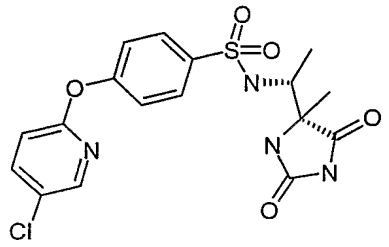
LC-MS(APCI): $M^+ + H^+ = 390.4$ *(m/z)*

4-(4-Chlorohenoxy-N-(1-(4-R-methyl-2,5-dioxoimidazolidin-4-R-yl)-ethyl benzenesulfonamide



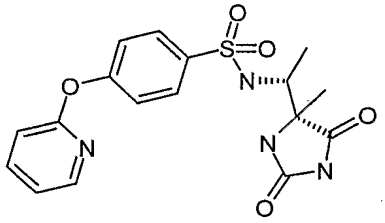
LC-MS(APCI): $M^+ + H^+ = 423.4$ *(m/z)*

4-(5-chloropyridyl-2-oxy)-N-(1-(4-R-methyl-2,5-dioxoimidazolidin-4-R-yl)-ethyl benzenesulfonamide



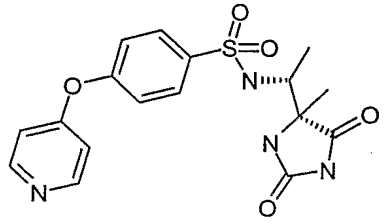
LC-MS(APCI): $M^+ + H^+ = 424.4$ *(m/z)*

N-(1-(4-R-methyl-2,5-dioxoimidazolidin-4-R-yl)-ethyl)-4-(pyridin-2-yloxy) benzenesulfonamide



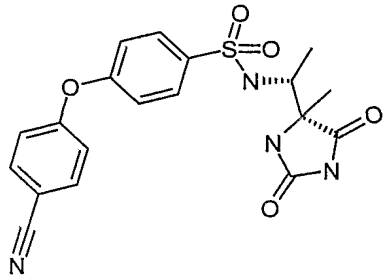
LC-MS(APCI): $M^+ + 2H^+ = 392.4$ *(m/z)*

N-(1-(4-R-methyl-2,5-dioxoimidazolidin-4-R-yl)-ethyl)-4-(pyridin-2-yloxy) benzenesulfonamide



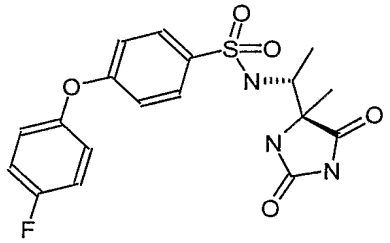
LC-MS(APCI): $M^+ + 2H^+ = 392.4$ *(m/z)*

4-(4-cyanophenoxy-N-(1-(4-R-methyl-2,5-dioxoimidazolidin-4-R-yl)-ethyl benzenesulfonamide



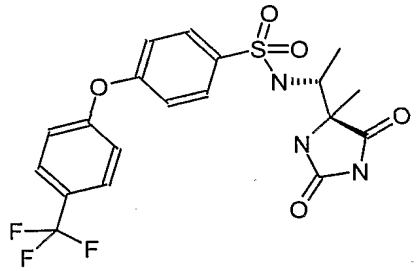
LC-MS(APCI): $M^+ + H^+ = 415.4$ *(m/z)*

4-(4-fluorophenoxy-N-(1-(4-R-methyl-2,5-dioxoimidazolidin-4-S-yl)-ethyl benzenesulfonamide



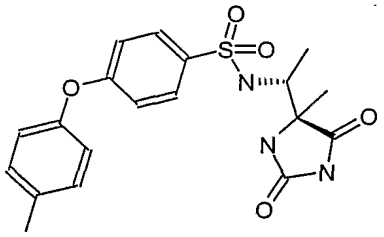
LC-MS(APCI): $M^+ + H^+ = 407.4$ *(m/z)*

4-(4-trifluoromethylphenoxy-N-(1-(4-R-methyl-2,5-dioxoimidazolidin-4-S-yl)-ethyl benzenesulfonamide



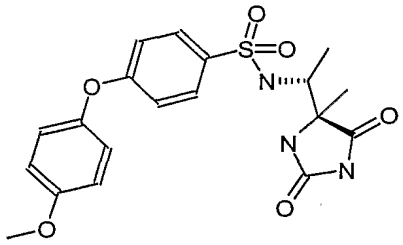
LC-MS(APCI): $M^+ + H^+ = 458.4$ *(m/z)*

4-(4-Methylphenoxy-N-(1-(4-R-methyl-2,5-dioxoimidazolidin-4-S-yl)-ethyl benzenesulfonamide



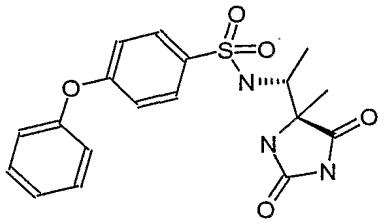
LC-MS(APCI): $M^+ + H^+ = 404.5$ *(m/z)*

4-(4-Methoxyphenoxy-N-(1-(4-R-methyl-2,5-dioxoimidazolidin-4-S-yl)-ethyl benzenesulfonamide



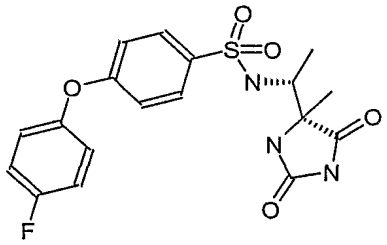
LC-MS(APCI): $M^+ + H^+ = 420.5$ *(m/z)*

4-(4-Phenoxy-N-(1-(4-R-methyl-2,5-dioxoimidazolidin-4-S-yl)-ethyl benzenesulfonamide



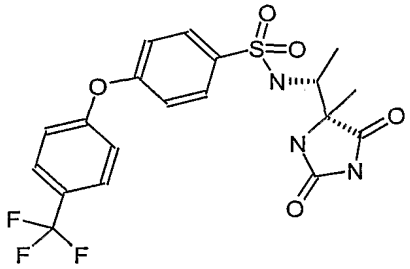
LC-MS(APCI): $M^+ + H^+ = 390.5$ *(m/z)*

4-(4-fluorophenoxy-N-(1-(4-R-methyl-2,5-dioxoimidazolidin-4-R-yl)-ethyl benzenesulfonamide



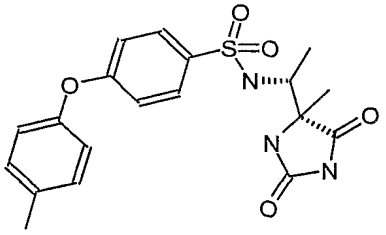
LC-MS(APCI): $M^+ + H^+ = 407.4$ *(m/z)*

4-(4-trifluoromethylphenoxy-N-(1-(4-R-methyl-2,5-dioxoimidazolidin-4-R-yl)-ethyl benzenesulfonamide



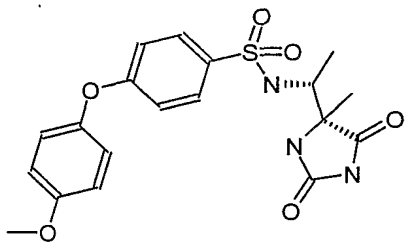
LC-MS(APCI): $M^+ + H^+ = 458.4$ *(m/z)*

4-(4-Methylphenoxy-N-(1-(4-R-methyl-2,5-dioxoimidazolidin-4-R-yl)-ethyl benzenesulfonamide



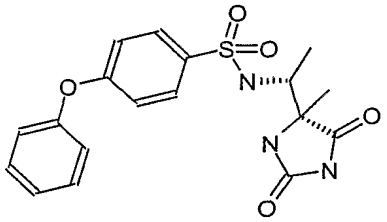
LC-MS(APCI): $M^+ + H^+ = 404.5$ *(m/z)*

4-(4-Methoxyphenoxy-N-(1-(4-R-methyl-2,5-dioxoimidazolidin-4-R-yl)-ethyl benzenesulfonamide



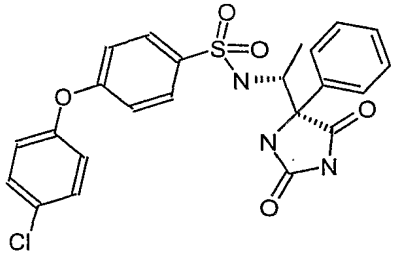
LC-MS(APCI): $M^+ + H^+ = 420.5$ *(m/z)*

4-(4-Phenoxy-N-(1-(4-R-methyl-2,5-dioxoimidazolidin-4-R-yl)-ethyl benzenesulfonamide



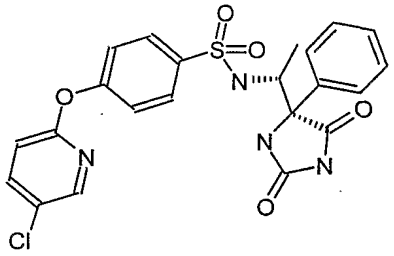
LC-MS(APCI): $M^+ + H^+ = 390.5$ *(m/z)*

4-(4-Chlorophenoxy)-N-(1-((2,5-dioxo-4-S-phenyl-imidazolidin-4-R-yl)-ethyl) benzenesuldonamide



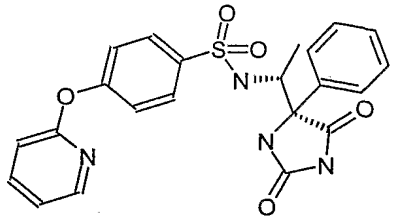
LC-MS(APCI): $M^+ + H^+ = 486.8$ *(m/z)*

4-(5-chloropyridin-2-yloxy)-N-(1-((2,5-dioxo-4-S-phenyl-imidazolidin-4-R-yl)-ethyl) benzenesuldonamide



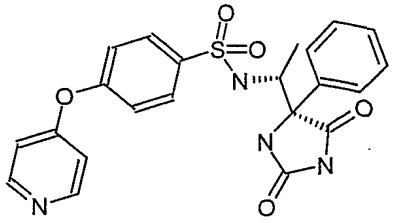
LC-MS(APCI): $M^+ + H^+ = 487.8$ *(m/z)*

N-(1-S-(2,5-dioxo-4-phenylimidazolidin-4-R-yl)-ethyl-4-(pyridin-2-yloxy)-benzenesulfonamide



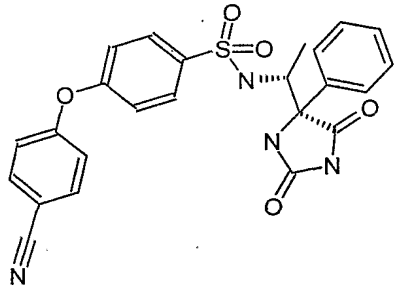
LC-MS(APCI): $M^+ + 2H^+ = 454.6$ *(m/z)*

N-(1-S-(2,5-dioxo-4-phenylimidazolidin-4-R-yl)-ethyl-4-(pyridin-4-yloxy)-benzenesulfonamide



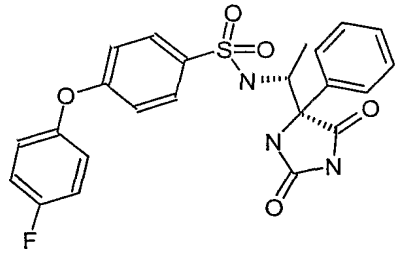
LC-MS(APCI): $M^+ + 2H^+ = 454.6$ *(m/z)*

4-(4-Cyanophenoxy)-N-(1-((2,5-dioxo-4-S-phenyl-imidazolidin-4-R-yl)-ethyl) benzenesulfonamide



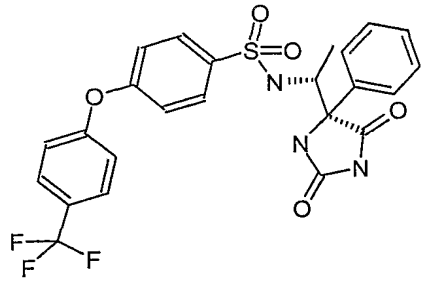
LC-MS(APCI): $M^+ + H^+ = 477.6$ *(m/z)*

4-(4-Fluorophenoxy)-N-(1-((2,5-dioxo-4-S-phenyl-imidazolidin-4-R-yl)-ethyl) benzenesulfonamide



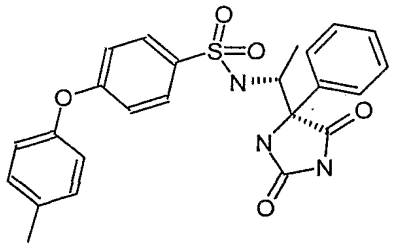
LC-MS(APCI): $M^+ + H^+ = 470.5$ *(m/z)*

4-(4-Trifluoromethylphenoxy)-N-(1-((2,5-dioxo-4-S-phenyl-imidazolidin-4-R-yl)-ethyl) benzenesulfonamide



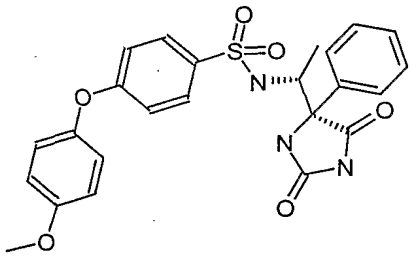
LC-MS(APCI): $M^+ + H^+ = 519.1$ *(m/z)*

4-(4-Methylphenoxy)-N-(1-((2,5-dioxo-4-S-phenyl-imidazolidin-4-R-yl)-ethyl) benzenesulfonamide



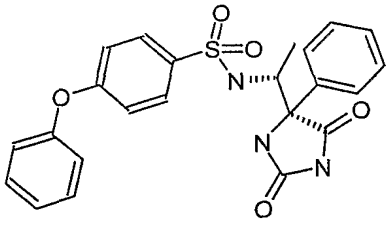
LC-MS(APCI): $M^+ + H^+ = 466.4$ *(m/z)*

4-(4-Methoxyphenoxy)-N-(1-((2,5-dioxo-4-S-phenyl-imidazolidin-4-R-yl)-ethyl) benzenesulfonamide



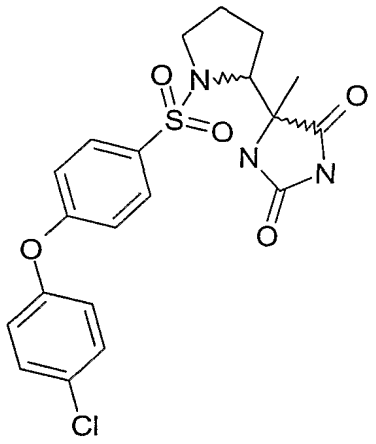
LC-MS(APCI): $M^+ + H^+ = 482.4$ *(m/z)*

4-(4-Phenoxy)-N-(1-((2,5-dioxo-4-S-phenyl-imidazolidin-4-R-yl)-ethyl) benzenesulfonamide



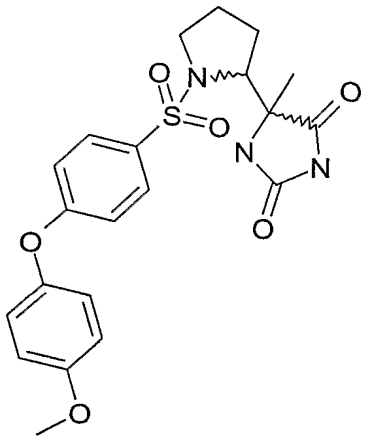
LC-MS(APCI): $M^+ + H^+ = 452.5$ *(m/z)*

5-(1-{[4-(4-chlorophenoxy)phenyl]sulfonyl}pyrrolidin-2-yl)-5-methylimidazolidine-2,4-dione



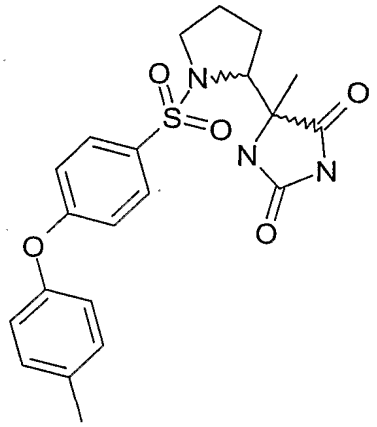
LC-MS(APCI): $M^+ + H^+ = 450.5$ *(m/z)*

5-(1-{[4-(4-methoxyphenoxy)phenyl]sulfonyl}pyrrolidin-2-yl)-5-methylimidazolidine-2,4-dione



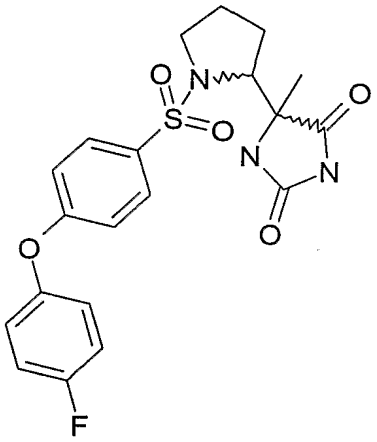
LC-MS(APCI): $M^+ + H^+ = 446.2$ *(m/z)*

5-(1-{[4-(4-methylphenoxy)phenyl]sulfonyl}pyrrolidin-2-yl)-5-methylimidazolidine-2,4-dione



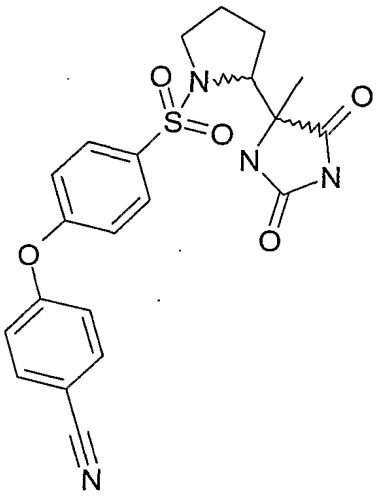
LC-MS(APCI): $M^+ + H^+ = 430.1$ *(m/z)*

5-(1-{[4-(4-fluorophenoxy)phenyl]sulfonyl}pyrrolidin-2-yl)-5-methylimidazolidine-2,4-dione



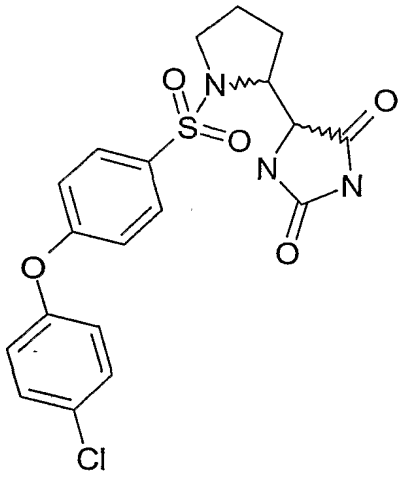
LC-MS(APCI): $M^+ + H^+ = 434.1$ *(m/z)*

(1-{[4-(4-cyanophenoxy)phenyl]sulfonyl}pyrrolidin-2-yl)-5-methylimidazolidine-2,4-dione



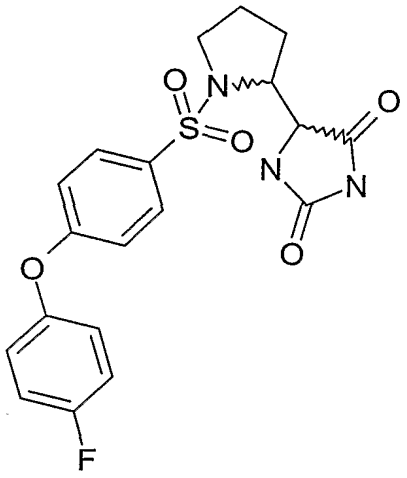
LC-MS(APCI): $M^+ + H^+ = 441.1$ *(m/z)*

5-(1-{[4-(4-chlorophenoxy)phenyl]sulfonyl}pyrrolidin-2-yl)imidazolidine-2,4-dione



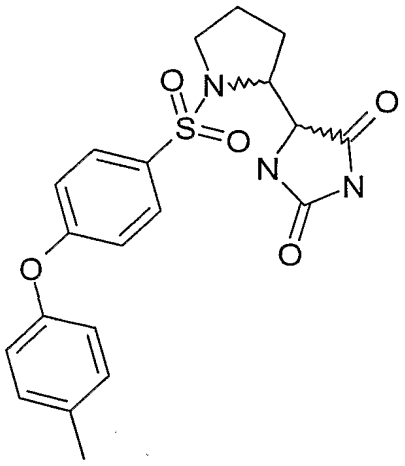
LC-MS(APCI): $M^+ + H^+ = 436.1$ *(m/z)*

5-(1-{[4-(4-fluorophenoxy)phenyl]sulfonyl}pyrrolidin-2-yl)imidazolidine-2,4-dione



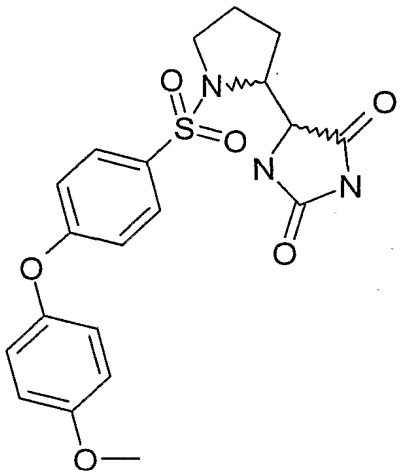
LC-MS(APCI): $M^+ + H^+ = 420.1$ *(m/z)*

5-(1-{[4-(4-methylphenoxy)phenyl]sulfonyl}pyrrolidin-2-yl)imidazolidine-2,4-dione



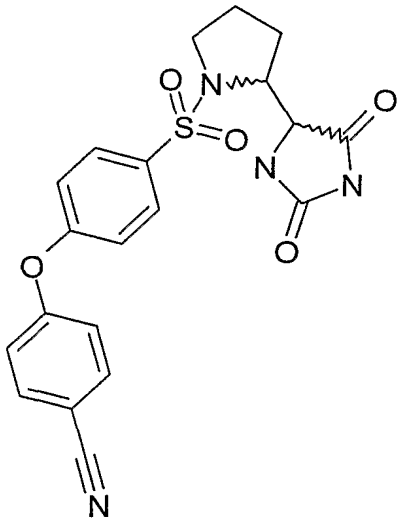
LC-MS(APCI): $M^+ + H^+ = 416.1$ *(m/z)*

5-(1-{[4-(4-methoxyphenoxy)phenyl]sulfonyl}pyrrolidin-2-yl)imidazolidine-2,4-dione



LC-MS(APCI): $M^+ + H^+ = 432.1$ *(m/z)*

5-(1-{[4-(4-cyanophenoxy)phenyl]sulfonyl}pyrrolidin-2-yl)imidazolidine-2,4-dione



LC-MS(APCI): $M^+ + H^+ = 427.1$ *(m/z)*

EXAMPLE 4

[(4*R*)-2,5-dioxoimidazolidinyl]methanesulfonyl chloride, [(4*S*)-2,5-dioxoimidazolidinyl]methanesulfonyl chloride or [(*R*)-2,5-Dioxoimidazolidinyl]-methanesulfonyl chloride was reacted with the appropriate primary or secondary amine to give the compounds listed below. All the amines employed are commercially available.

Sulfonyl chloride (0.060 mmoles), amine (0.060 mmoles), triethylamine (0.0084 mL, 0.060 mmoles) in dry tetrahydrofuran (0.70 mL) were stirred at room temperature over night. Polystyrene methylisocyanate (0.025 g, 0.030 mmoles) was added and the mixture was shaken over night. The white suspension was filtered and the solids were rinsed with tetrahydrofuran (2x1 mL). The filtrates were evaporated, the white solid was suspended in water (5 mL), collected on a filter, washed with water (2x1 mL), sucked free of water and dried in vacuo at 45°C over night to afford the title compounds.

The starting materials were prepared as follows:

5-methyl-5-{[(phenylmethyl)thio]methyl}imidazolidine-2,4-dione

A steel vessel was charged with ethanol and water (315mL/135mL).
31.7g (0.175 mol) of benzylthioacetone, 22.9g (0.351 mol) of potassium cyanide and 84.5g (0.879 mol) of ammonium carbonate was added. The closed reaction vessel was kept in an oil bath (bath temperature 90 °C) under vigorous stirring for 3h.
The reaction vessel was cooled with ice-water (0.5 h), the yellowish slurry was evaporated to dryness and the solid residue partitioned between 400 mL water and 700 mL ethylacetate and separated. The water-phase was extracted with ethylacetate (300 mL). The combined organic phases were washed with saturated brine (150 mL), dried (Na_2SO_4), filtered and evaporated to dryness. If the product did not crystallize, 300 mL of dichloromethane was added to the oil. Evaporation gave the product as a slightly yellowish powder,43.8 g (90%).

LC-MS (APCI) m/z 251.1 (MH+).

^{1}H NMR (DMSO-d_6) δ: 10.74 (1H,s); 8.00 (1H, s); 7.35-7.20 (5H, m); 3.76 (2H, s); 2.72, 2.62 (1H each, ABq, *J*=14.0 Hz); 1.29 (3H, s).

^{13}C NMR (DMSO-d_6) δ: 177.30, 156.38, 138.11, 128.74, 128.24, 126.77, 62.93, 37.96, 36.39, 23.15.

(5*S*)-5-methyl-5-{[(phenylmethyl)thio]methyl}imidazolidine-2,4-dione

The title compound was prepared by chiral separation of the racemic material using a 250mm x 50mm column on a Dynamic Axial Compression Preparative HPLC system. The stationary phase used was CHIRALPAK AD, eluent=Methanol, flow=89mL/min, temp=ambient, UV=220nm, sample conc=150mg/mL, injection volume=20mL.
Retention time for title compound = 6 min.
Analysis of chiral purity was made using a 250mm x 4.6mm CHIRALPAK-AD column from Daicel, flow=0.5mL/min, eluent=Ethanol, UV=220nm, temp=ambient.
Retention time for title compound = 9.27min.
Purity estimated to >99% ee.
LC-MS (APCI) m/z 251.1 (MH+).
$[\alpha]_D$=-30.3° (c=0.01g/mL, MeOH, T=20°C).
^{1}H NMR (DMSO-d_6) δ: 10.74 (1H,s); 8.00 (1H, s); 7.35-7.20 (5H, m); 3.76 (2H, s); 2.72, 2.62 (1H each, ABq, *J*=14.0 Hz); 1.29 (3H, s).
^{13}C NMR (DMSO-d_6) δ: 177.30, 156.28, 138.11, 128.74, 128.24, 126.77, 62.93, 37.96, 36.39, 23.15.

(5*R*)-5-methyl-5-{[(phenylmethyl)thio]methyl}imidazolidine-2,4-dione

The title compound was prepared by chiral separation of the racemic material using a 250mm x 50mm column on a Dynamic Axial Compression Preparative HPLC system. The stationary phase used was CHIRALPAK AD, eluent=Methanol, flow=89mL/min, temp=ambient, UV=220nm, sample conc=150mg/mL, injection volume=20mL.
Retention time for title compound = 10 min.

Analysis of chiral purity was made using a 250mm x 4.6mm CHIRALPAK-AD column from Daicel, flow=0.5mL/min, eluent=Ethanol, UV=220nm, temp=ambient.
Retention time for title compound = 17.81 min.
Chiral purity estimated to >99% ee.
LC-MS (APCI) m/z 251.0 (MH+).
$[\alpha]_D$=+30.3° (c=0.01g/mL, MeOH, T=20°C).
^{1}H NMR (DMSO-d_6) δ: 10.74 (1H,s); 8.00 (1H, s); 7.35-7.20 (5H, m); 3.76 (2H, s); 2.72, 2.62 (1H each, ABq, *J*=14.0 Hz); 1.29 (3H, s).
^{13}C NMR (DMSO-d_6) δ: 177.31, 156.30, 138.11, 128.74, 128.25, 126.77, 62.94, 37.97, 36.40, 23.16.

[(4*S*)-4-methyl-2,5-dioxoimidazolidin-4-yl]methanesulfonyl chloride

(5S)-5-methyl-5-{[(phenylmethyl)thio]methyl}imidazolidine-2,4-dione (42.6g; 0.17mol) was dissolved in a mixture of AcOH (450 mL) and H_2O (50 mL). The mixture was immersed in an ice/water bath, Cl_2 (g) was bubbled through the solution, the flow of gas was adjusted so that the temperature was kept below +15 °C. After 25 min the solution became yellow-green in colour and a sample was withdrawn for LC/MS and HPLC analysis. It showed that starting material was consumed. The yellow clear solution was stirred for 30 min and an opaque solution /slurry was formed.
The solvent was removed on a rotary evaporator using waterbath with temperature held at +37°C. The yellowish solid was suspended in Toluene (400mL) and solvent removed on the same rotary evaporator. This was repeated once more.
The crude product was then suspended in iso-Hexane (400mL) and warmed to +40°C while stirring, the slurry was allowed to cool to room temperature before the insoluble product was removed by filtration, washed with iso-Hexane (6x100mL), and dried under reduced preassure at +50°C over night. This gave the product as a slightly yellow powder.
Obtained 36.9 g (95%) of the title compound.
Purity by HPLC = 99%, NMR supported that purity.
$[\alpha]_D$=-12.4° (c=0.01g/mL, THF, T=20°C).

^{1}H NMR (THF-d_8): δ 9.91 (1H, bs); 7.57 (1H, s); 4.53, 4.44 (1H each, ABq, *J*=14.6Hz); 1.52 (s, 3H, CH_3).

^{13}C NMR (THF-d_8): δ 174.96; 155.86; 70.96; 61.04; 23.66.

[(4*R*)-4-methyl-2,5-dioxoimidazolidin-4-yl]methanesulfonyl chloride

Following the procedure described for [(4S)-4-methyl-2,5-dioxoimidazolidin-4-yl]methanesulfonyl chloride.

Starting from (5R)-5-methyl-5-{[(phenylmethyl)thio]methyl}imidazolidine-2,4-dione (10.0g, 40mmol).

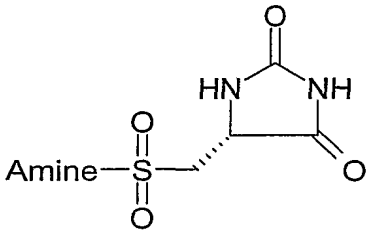
Obtained 8.78g (96% yield) of the title compound.

Purity by NMR > 98%.

$[\alpha]_D$=+12.8° (c=0.01g/mL, THF, T=20°C).

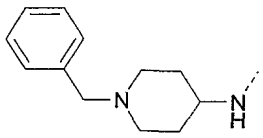
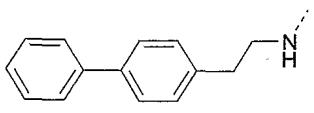
^{1}H NMR (THF-d_8): δ 9.91 (1H, brs); 7.57 (1H, s); 4.53, 4.44 (1H each, ABq, *J*=14.6Hz); 1.52 (s, 3H, CH_3).

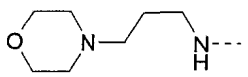
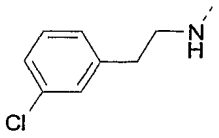
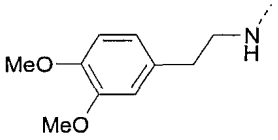
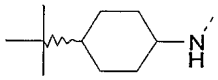
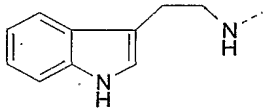
^{13}C NMR (THF-d_8): δ 174.96; 155.84; 70.97; 61.04; 23.66.

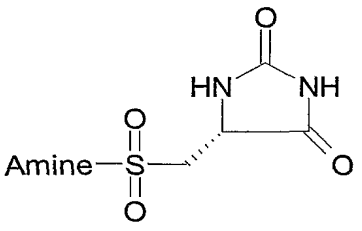


(R)-

The Table below gives the Amine group for each compound of the above structure.

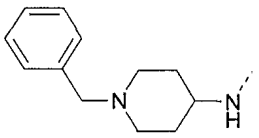
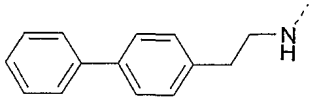
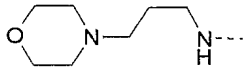
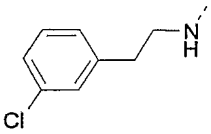
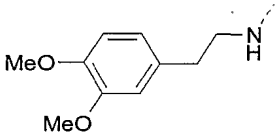
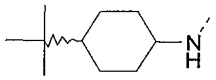
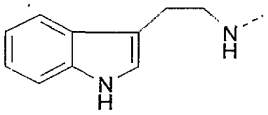
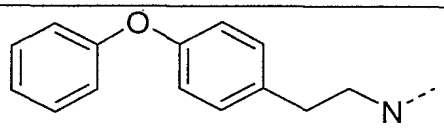
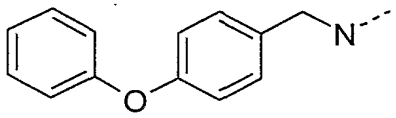
 MW. 366 m/z 367 (M+1)	 MW. 373.43 m/z 374 (M+1)

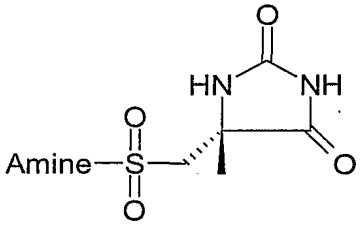
 MW.320 m/z 321 (M+1)	 MW. 331.78 m/z 332 (M+1)
 MW. 357.39 m/z 358 (M+1)	 MW. 331.44 m/z 332 (M+1)
 MW. 336.37 m/z 337 (M+1)	



(S)-

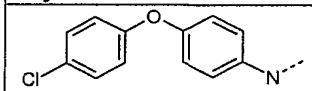
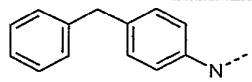
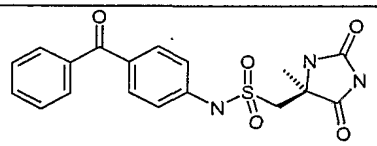
The Table below gives the Amine group for each compound of the above structure.

 MW. 366 m/z 367 (M+1)	 MW. 373.43 m/z 374 (M+1)
 MW.320 m/z 321 (M+1)	 MW. 331.78 m/z 332 (M+1)
 MW. 357.39 m/z 358 (M+1)	 MW. 331.44 m/z 332 (M+1)
 MW. 336.37 m/z 337 (M+1)	 MW. 403.46 m/z 404 (M+1)
 MW. 389.43 m/z 390 (M+1)	



(S)-

The Table below gives the Amine group for each compound of the above structure.

Hydantoin	Analysis[1]
	MW. 375.41 m/z 410 (MH+)
	m/z 374 (MH+) MW. 373.43
	m/z 388 (MH+) MW. 387.42

***N*-[4-(4-Chloro-phenoxy)-phenyl]-*C*-((4*S*)-4-methyl-2,5-dioxo-imidazolidin-4-yl)-methanesulfonamide**

LC-MS (APCI) m/z 410 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.75 (1 H, s); 9.89 (1 H, s); 8.04 (1 H, s); 7.45-7.39 (2 H, m); 7.25-7.19 (2 H, m); 7.06-6.97 (4 H, m); 3.54 (1 H from ABq, *J*=14.1 Hz); 1.31 (3 H, s).

***N*-(4-Benzyl-phenyl)-*C*-((4*S*)-4-methyl-2,5-dioxo-imidazolidin-4-yl)-methanesulfonamide**

LC-MS (APCI) m/z 374 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.74 (1 H, s); 9.82 (1 H, s); 8.01 (1 H, s); 7.33-7.05 (9 H, m); 3.49, 3.36 (1 H each, ABq, *J*=16.2 Hz); 1.28 (3 H, s).

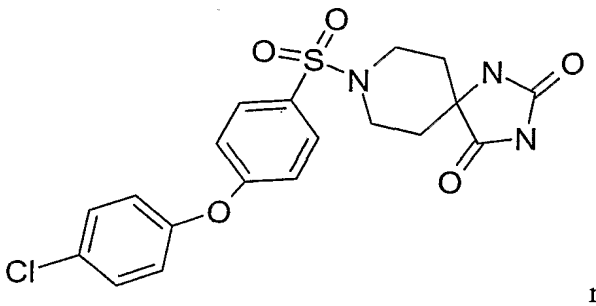
***N*-(4-Benzoyl-phenyl)-*C*-((4*S*)-4-methyl-2,5-dioxo-imidazolidin-4-yl)-methanesulfonamide**

LC-MS (APCI) m/z 388 (MH+).

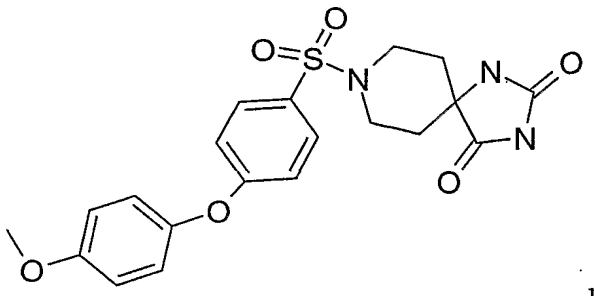
^{1}H NMR (DMSO- d_6): δ 10.81 (1 H, s); 10.58 (1 H, s); 8.08 (1 H, s); 7.76-7.62 (5 H, m); 7.60-7.52 (2 H, m); 7.33-7.27 (2 H, m); 3.68, 3.52 (1 H each, ABq, *J*=14.7 Hz); 1.33 (3 H, s).

EXAMPLE 5

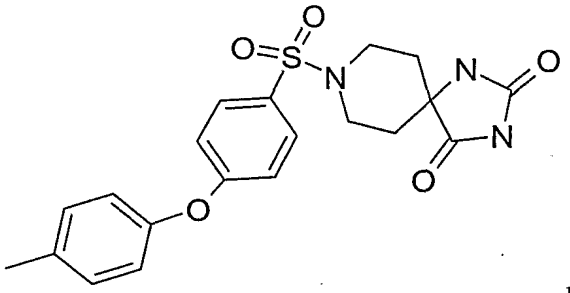
Prepared from commercially available N-Boc-4-piperidone by methods described in Example 3.



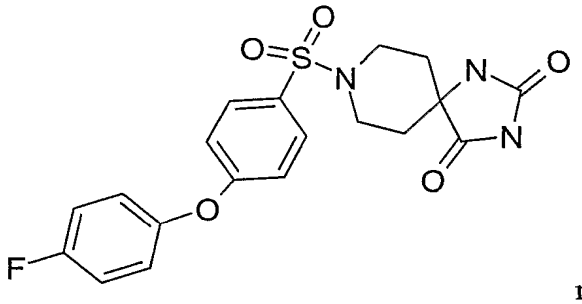
m/z 437 (MH+) MW. 435.89



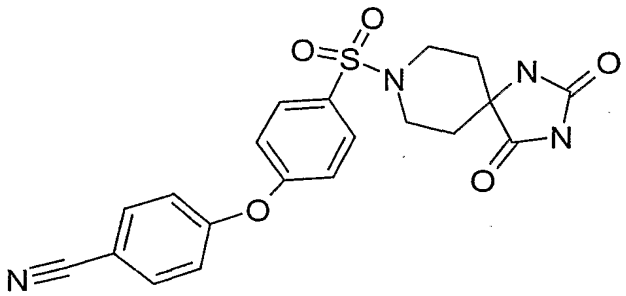
m/z 432 (MH+) MW. 431.47



m/z 416 (MH+) MW. 415.47



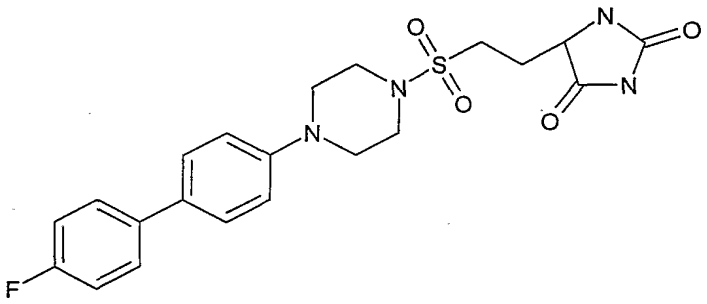
m/z 420 (MH+) MW. 419.43



m/z 427 (MH+) MW. 426.45

EXAMPLE 6

5-(2-{[4-(4'-fluoro[1,1'-biphenyl]-4-yl)-1-piperazinyl]sulfonyl}ethyl)-2,4-imidazolidinedione



To the solution of 1-(4-fluorophenyl)-phenylpiperazin (0.125 mg ,0.48 mmol) in 5 ml of dichloromethane was added triethylamin (0.06 ml, 0.5 mmol) and 2-(2,5-dioxo-4-imidazolidinyl)-1-ethanesulfonyl chloride (0.113 ml 0.48 mol). The mixture was stirred for 18 hrs,diluted with DCM to 25 ml,extracted with 1N HCl (5 ml) sat.NaHCO3 (5 ml) and dried,evaporated,crystallised (EtOH-dioxan).

LC-MS (APCI) m/z 446.9 (MH+).

1H NMR δ 1.95m (1H); 2.1m (1.15H),3.2 m(13.3H),4.1m (1H),7.05d (2H),7.25d(2.1H),7.65d (2.2H),7.80d(1.8H),8.0 bs (NH).

The starting materials were prepared as follows:

2-(2,5-dioxo-4-imidazolidinyl)-1-ethanesulfonyl chloride

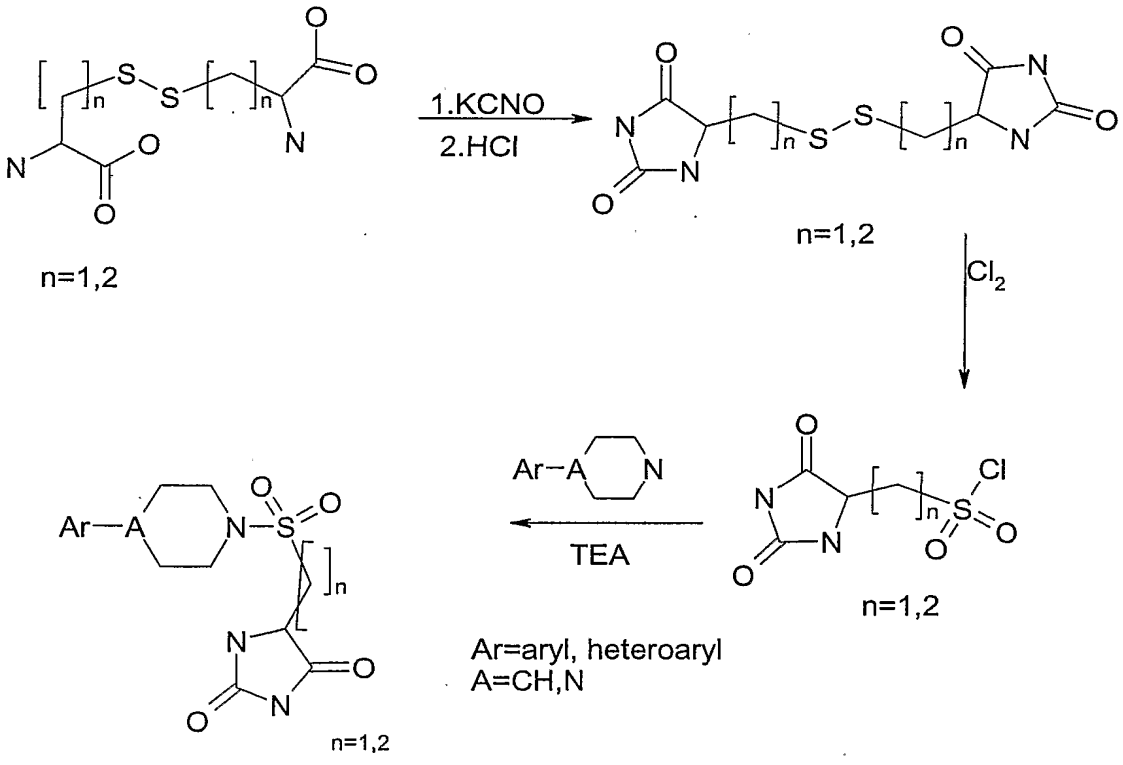
To the suspension of 5-(2-{[2-(2,5-dioxo-4-imidazolidinyl)ethyl]disulfanyl}ethyl)-2,4-imidazolidinedione (6.9 mol) in the mixture of 25 ml AcOH and 2 ml water stirred violently in three necked flask with gas-inlet tube,thermometer and short reflux condenser,placed in the ice bath,was bubbled chlorine gas for 15 min (until all precipitate dissolved) at max.temp.+5°C.Then,it was stirred 15 min more,evaporated to a small volume in vacuo (max.temp 30°C),dissolved in 50 ml of dichloromethane,shaken carefully

with sat.NaHCO3 (ca 25 ml),then with 10% sodium thiosulfate, dried, evaporated, crystallised from THF-hexane (Lora-Tamayo, M. *et al*, 1968, An. Quim., 64(6):591-606); ^{1}H NMR : δ 2.55m (1.1H),2.65m (1.8H),2.70m (1H),4.55m (1H).

5-(2-{[2-(2,5-dioxo-4-imidazolidinyl)ethyl]disulfanyl}ethyl)-2,4-imidazolidinedione

Commercially available RS homocystine (0.18 mol) was suspended in 25 ml water and of potassium cyanate 1.5 g (0.2 mol) was added and the mixture was stirred at 100°C for 45 min.Then it was allowed to cool partially and 10 ml of 10% HCl were added at once and the mixture was stirred at 100°C again for 50 min.It was placed in the fridge overnight,crystals were filtered and washed successively with water and dried in vacuo. LC-MS (APCI) m/z 319.1 (MH+).

The overall generalised reaction scheme is shown below:



EXAMPLE 7

(5*R*)-5-{[(4-phenyl-1-piperazinyl)sulfonyl]methyl}-2,4-imidazolidinedione

The title compound was prepared according to the scheme shown in Example 6.

To the solution of R-(2,5-dioxo-4-imidazolidinyl)methanesulfonyl chloride (100 mg,0.47 mmol) in 2.5 ml THF was added the solution of 1-phenylpiperazine (85 mg,0.52 mmol) and 65 ul of triethylamine (0.52 mmol) in 2.5 ml THF via syringe at once. The mixture was stirred for 3 hrs, precipitated triethylammonium chloride was filtered, washed with two small portions of THF, evaporated and recrystallised from EtOH and a small amount of AcOH.

LC-MS (APCI) m/z 339.1 (MH+).

^{1}H NMR δ 2.5 m (2H),3.1bs(6.5H),3.3m(2.5H),4.55m (1H),6.8 t(1H),6.9d(1.88H),7.2 t(2.05H),9.1 bs (1.7H).

The starting materials were prepared as follows:

R-(2,5-dioxo-4-imidazolidinyl)methanesulfonyl chloride

To the suspension of R-5-({[(2,5-dioxo-4-imidazolidinyl)methyl]disulfanyl}methyl)-2,4-imidazolidinedione (6.9 mol) in the mixture of 25 ml AcOH and 2 ml water stirred violently in three necked flask with gas-inlet tube,thermometer and short reflux condenser,placed in the ice bath,was bubbled chlorine gas for 15 min (until all precipitate dissolved) at max.temp.+5°C.Then,it was stirred 15 min more,evaporated to a small volume in vacuo (max.temp 30°C),dissolved in 50 ml of dichloromethane,shaken carefully with sat.NaHCO3 (ca 25 ml),then with 10% sodium thiosulfate, dried, evaporated, crystallised from THF-hexane (Lora-Tamayo, M. *et al*, 1968, An. Quim., 64(6):591-606);

^{1}H NMR (DMSO-d_6): δ 3.21m (1.1H),3.3m (0.7H).4,65m (1H).

R-5-({[(2,5-dioxo-4-imidazolidinyl)methyl]disulfanyl}methyl)-2,4-imidazolidinedione

Commercially available R cystine (0.18 mol) was suspended in 25 ml water and of potassium cyanate 1.5 g (0.2 mol) was added and the mixture was stirred at 100°C for 45

min.Then it was allowed to cool partially and 10 ml of 10% HCl were added at once and the mixture was stirred at 100°C again for 50 min.It was placed in the fridge overnight,crystals were filtered and washed successively with water and dried in vacuo. LC-MS (APCI) m/z 291 (MH+).

EXAMPLE 8

(5S)-5-{[(4-phenyl-1-piperazinyl)sulfonyl]methyl}-2,4-imidazolidinedione

The title compound was prepared according to the scheme shown in Example 6.

To the solution of S-(2,5-dioxo-4-imidazolidinyl)methanesulfonyl chloride (100 mg,0.47 mmol) in 2.5 ml THF was added the solution of 1-phenylpiperazine (85 mg,0.52 mmol) and 65 ul of triethylamine (0.52 mmol) in 2.5 ml THF via syringe at once.The mixture was stirred for 3 hrs, precipitated triethylammonium chloride was filtered, washed with two small portions of THF, evaporated and recrystallised from EtOH and a small amount of AcOH.

LC-MS (APCI) m/z 339.1 (MH+).

^{1}H NMR: δ 2.5 m (2H),3.1bs(6.5H),3.3m(2.5H),4.55m (1H),6.8 t(1H),6.9d(1.88H),7.2 t(2.05H),9.1 bs (1.7H)

The starting materials were prepared as follows:

S-(2,5-dioxo-4-imidazolidinyl)methanesulfonyl chloride

To the suspension of S-5-({[(2,5-dioxo-4-imidazolidinyl)methyl]disulfanyl}methyl)-2,4-imidazolidinedione (6.9 mol) in the mixture of 25 ml AcOH and 2 ml water stirred violently in three necked flask with gas-inlet tube,thermometer and short reflux condenser,placed in the ice bath,was bubbled chlorine gas for 15 min (until all precipitate dissolved) at max.temp.+5°C.Then,it was stirred 15 min more,evaporated to a small volume in vacuo (max.temp 30°C),dissolved in 50 ml of dichloromethane,shaken carefully with sat.NaHCO3 (ca 25 ml),then with 10% sodium thiosulfate, dried, evaporated, crystallised from THF-hexane (Lora-Tamayo, M. *et al*, 1968, An. Quim., 64(6):591-606);

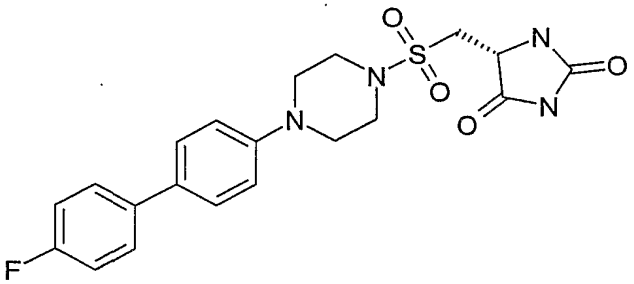
^{1}H NMR (DMSO-d_6): δ 3.2m (0.9H,3.35m (0.9H),4.50m (1H).

S-5-({[(2,5-dioxo-4-imidazolidinyl)methyl]disulfanyl}methyl)-2,4-imidazolidinedione

Commercially available S cystine (0.18 mol) was suspended in 25 ml water and of potassium cyanate 1.5 g (0.2 mol) was added and the mixture was stirred at 100°C for 45 min.Then it was allowed to cool partially and 10 ml of 10% HCl were added at once and the mixture was stirred at 100°C again for 50 min.It was placed in the fridge overnight,crystals were filtered and washed successively with water and dried in vacuo. LC-MS (APCI) m/z 291.1 (MH+).

EXAMPLE 9

(*R*)-5-(([4-(4′-fluoro[1,1′-biphenyl]-4-yl)-1-piperazinyl]sulfonyl)methyl)-2,4-imidazolidinedione



[(*R*)-2,5-Dioxoimidazolidinyl]methanesulfonyl chloride (0.0127 g, 0.060 mmol), 1-(4′-fluoro[1,1′-biphenyl]-4-yl)piperazine (0.0154 g, 0.060 mmol), triethylamine (0.0084 mL, 0.060 mmol) and dry tetrahydrofuran (0.70 mL) were stirred at room temperature over

night. Polystyrene methylisocyanate (0.025 g, 0.030 mmol) was added and the mixture was shaken over night. The white suspension was carefully transferred to a round-bottomed flask, the resin was rinsed with tetrahydrofuran (2x1 mL) and washings were transferred to the bulk of suspension. The solvent was evaporated, the white solid was suspended in water (5 mL), collected on a filter, washed with water (2x1 mL), sucked free of water and dried in vacuo at 45°C over night to afford approx. 0.010 g of the title compound.
LC-MS (APCI) m/z 434 (MH+).
^{1}H NMR (DMSO-d_6) δ 10.8 (1H, bs), 7.98 (1H, d, *J*=2Hz), 7.63 (2H, dd, J_1=5Hz, J_2=9Hz), 7.53 (2H, d, *J*=9Hz), 7.23 (2H, t, *J*=9Hz), 7.05 (2H, d, *J*=9Hz), 4.45 (1H, ddd, J_1=2Hz, J_2=4Hz, J_3=6Hz), 3.51 (1H, dd, J_1=15Hz, J_2=7Hz), 3.44 (1H, dd, J_1=15Hz, J_2=4Hz), 3.35-3.25 (8H, m´s; obscured by water signal) ppm.
^{13}C NMR (DMSO-d_6) δ 173.7, 161.3 (d, *J*=243Hz), 157.3, 149.8, 136.4 (d, *J*=3Hz), 130.1, 127.7 (d, *J*=8Hz), 127.2, 116.2, 115.5 (d, *J*=21Hz), 53.4, 49.4, 48.0, 44.9.

The starting materials were prepared as follows:

[(*R*)-2,5-Dioxoimidazolidinyl]methanesulfonyl chloride was prepared according to Mosher *et al*, 1958, J. Org. Chem 23:1257.

1-(4´-Fluoro[1,1´-biphenyl]-4-yl)piperazine
4-Bromo-4´-fluorobiphenyl (4.46 g, 17.8 mmol), N-*tert*-butoxycarbonyl piperazine (3.97 g, 21.3 mmol), sodium *tert*-butoxide (2.39 g, 24.9mmol), racemic 2,2´-bis(diphenylphosphino)-1,1´-binaphthyl (*rac*-BINAP) (0.082 g, 0.131 mmol), bis-(dibenzylideneacetone)palladium (0) (0.041 g, 0.045 mmol) and dry toluene (45 mL) were stirred at 80°C under nitrogen atmosphere for six hours. The warm mixture was filtered, the solids were washed twice with warm toluene and the filtrate was concentrated in vacuo giving an orange-red crude, which was stirred with ether (50mL) for two hours. The solid was filtered off, washed with small volumes of ether and dried in vacuo at 45°C over night

to give 5.57 g (88% yield) of *tert*-butyl 4-(4′-fluoro[1,1′-biphenyl]-4-yl)-1-piperazinecarboxylate. This product (5.52 g, 15.5 mmol) was dissolved in dioxane (150 mL) and stirred with 4M hydrochloric acid (8.1 mL) at RT over night. Concentrated hydrochloric acid (3.0 mL) was added and stirring was continued at 45°C for 1.5 hours and at 60°C for 1 hour. The solution was concentrated to dryness and the solid was triturated with ether (100 mL), filtered, washed with small volumes of ether and dried in vacuo at 45°C for two hours to give 5.26 g (103% yield) of 1-(4′-fluoro[1,1′-biphenyl]-4-yl)piperazine dihydrochloride as a light-yellow salt.

LC-MS (APCI) m/z 257 (MH+).

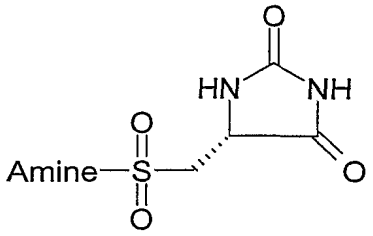
^{1}H NMR (DMSO-d_6) δ 9.40 (2H, bs), 7.64 (2H, dd, J_1=6Hz, J_2=9Hz), 7.55 (2H, d, J=9Hz), 7.24 (2H, t, J=9Hz), 7.07 (2H, d, J=9Hz), 3.46-3.41 (4H, m), 3.25-3.17 (4H, m).

The salt was treated with aqueous sodium hydroxide solution and the base was taken up in dichloro-methane. Drying with Na_2SO_4, filtering and concentrating the organic phase gave the title compound as an offwhite solid.

^{1}H NMR (DMSO-d_6) δ 7.61 (2H, dd, J_1=6Hz, J_2=9Hz), 7.49 (2H, d, J=9Hz), 7.22 (2H, t, J=9Hz), 6.98 (2H, d, J=9Hz), 3.10-3.06 (4H, m), 2.86-2.81 (4H, m).

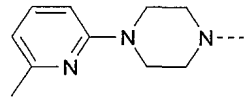
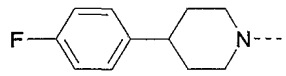
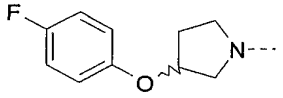
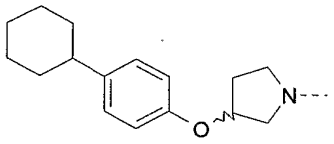
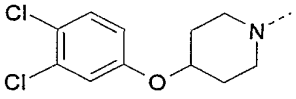
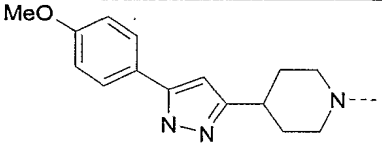
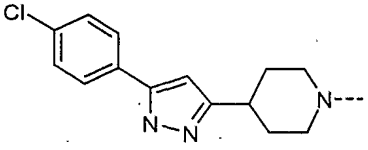
EXAMPLE 10

Using an analogous procedure to that described in Example 9, [(4*R*)-2,5-dioxoimidazolidinyl]methanesulfonyl chloride was reacted with the appropriate primary or secondary amine to give the compounds listed below. All the amines employed are commercially available.



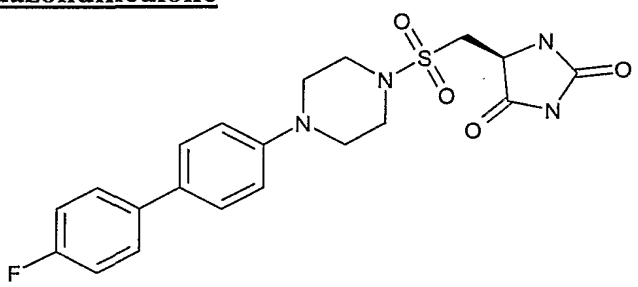
(R)-

The Table below gives the Amine group for each compound of the above structure.

 MW. 353.40 m/z 354 (MH+)	 MW. 355.39 m/z 356 (MH+)
 MW. 357.36 m/z 358 (MH+)	 MW. 421.52 m/z 422 (MH+)
 MW. 422.29 m/z 423 (MH+)	 MW. 433.49 m/z 434 (MH+)
 MW. 437.91 m/z 438 (MH+)	

EXAMPLE 11

(*S*)-5-(([4-(4′-fluoro[1,1′-biphenyl]-4-yl)-1-piperazinyl]sulfonyl)methyl)-2,4-imidazolidinedione



[(*S*)-2,5-Dioxoimidazolidinyl]methanesulfonyl chloride (0.0127 g, 0.060 mmol), 1-(4′-fluoro[1,1′-biphenyl]-4-yl)piperazine (0.0154 g, 0.060 mmol), triethylamine (0.0084 mL, 0.060 mmol) and dry tetrahydrofuran (0.70 mL) were stirred at room temperature over night. Polystyrene methylisocyanate (0.025 g, 0.030 mmol) was added and the mixture was shaken over night. The white suspension was carefully transferred to a round-bottomed flask, the resin was rinsed with tetrahydrofuran (2x1 mL) and washings were transferred to the bulk of suspension. The solvent was evaporated, the white solid was suspended in water (5 mL), collected on a filter, washed with water (2x1 mL), sucked free of water and dried in vacuo at 45°C over night to afford approx. 0.010 g of the title compound.

LC-MS (APCI) m/z 433 (MH+).

^{1}H NMR (DMSO-d_6) δ 10.8 (1H, br s), 7.98 (1H, d, J=2Hz), 7.63 (2H, dd, J_1=5Hz, J_2=9Hz), 7.53 (2H, d, J=9Hz), 7.23 (2H, t, J=9Hz), 7.05 (2H, d, J=9Hz), 4.45 (1H, ddd, J_1=2Hz, J_2=4Hz, J_3=6Hz), 3.51 (1H, dd, J_1=15Hz, J_2=7Hz), 3.44 (1H, dd, J_1=15Hz, J_2=4Hz), 3.35-3.25 (8H, m′s; obscured by water signal).

^{13}C NMR (DMSO-d_6) δ 173.7, 161.3 (d, J=243Hz), 157.3, 149.8, 136.4 (d, J=3Hz), 130.1, 127.7 (d, J=8Hz), 127.2, 116.2, 115.5 (d, J=21Hz), 53.4, 49.4, 48.0, 44.9.

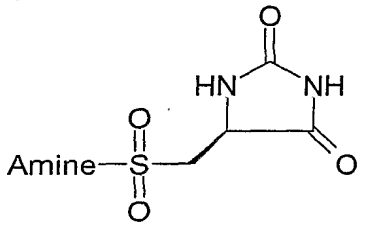
The starting materials were prepared as follows:

[(*S*)-2,5-Dioxoimidazolidinyl]methanesulfonyl chloride was prepared according to Mosher *et al*, 1958, J. Org. Chem 23:1257.

1-(4′-Fluoro[1,1′-biphenyl]-4-yl)piperazine was prepared according to Example 9.

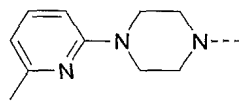
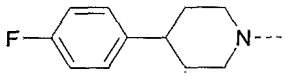
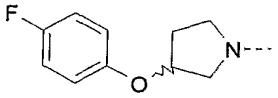
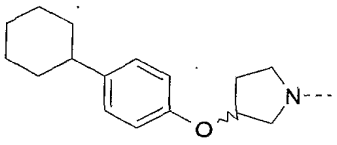
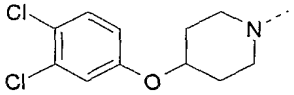
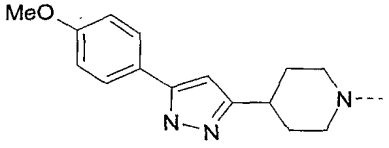
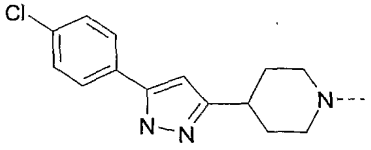
EXAMPLE 12

Using an analogous procedure to that described in Example 11, [(4*S*)-2,5-dioxoimidazolidinyl]methanesulfonyl chloride was reacted with the appropriate primary or secondary amine to give the compounds listed below. All the amines employed are commercially available.



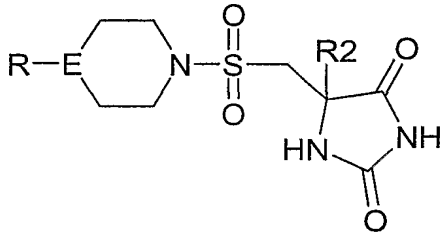
(S)-

The Table below gives the Amine group for each compound of the above structure.

 MW. 353.40 m/z 354 (MH+)	 MW. 355.39 m/z 356 (MH+)
 MW. 357.36 m/z 358 (MH+)	 MW. 421.52 m/z 422 (MH+)
 MW. 422.29 m/z 423 (MH+)	 MW. 433.49 m/z 434 (MH+)
 MW. 437.91 m/z 438 (MH+)	

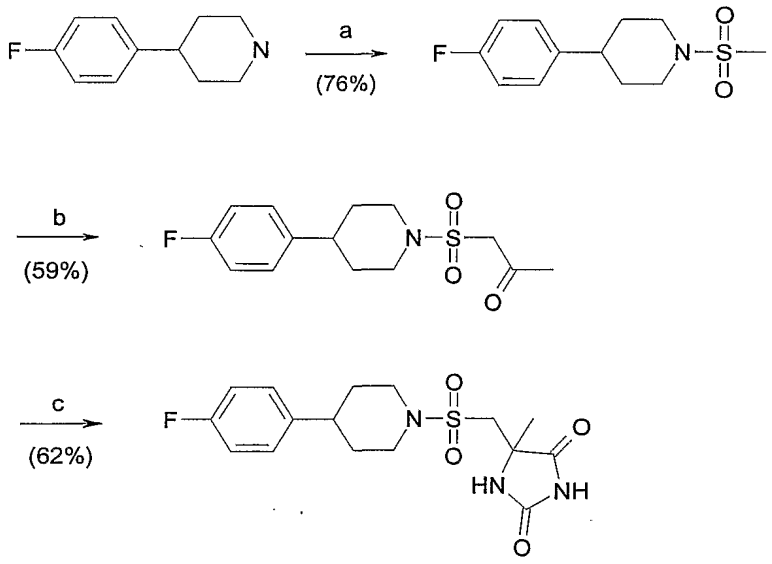
EXAMPLE 13

Hydantoins with the following general structure were synthesised (where E is carbon or a heteroatom):



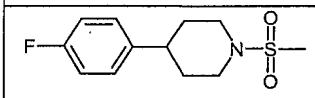
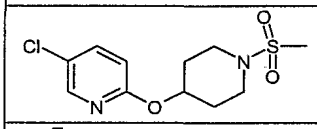
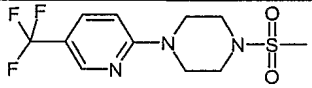
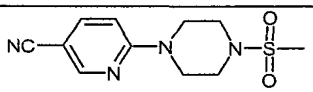
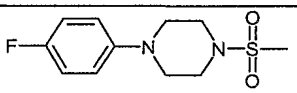
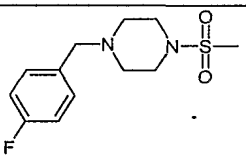
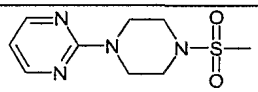
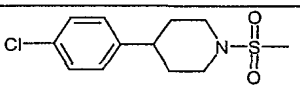
Representative synthetic route:

(5R,S)-5-[4-(4-Fluoro-phenyl)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione.



Reagents: a) $MeSO_2Cl$, DCM, 0°C, 2.5h. b) i. LHMDS, THF, 45min. ii. MeOAc, THF, 40min. c) KCN, $(NH_4)_2CO_3$, 50%EtOH/H_2O, 70°C, 17h.

SULFONYL-AMIDE INTERMEDIATES

Structure	Analysis [1]
	m/z 258 (MH+)
	m/z 291 (MH+)
	m/z 310 (MH+)
	m/z 267 (MH+)
	m/z 259 (MH+)
	m/z 273 (MH+)
	m/z 243 (MH+)
	m/z 274 (MH+)

[1]: For NMR-data see experimental part.

4-(4-Fluoro-phenyl)-1-methanesulfonyl-piperidine

4-(4-Fluoro-phenyl)piperidine hydrochloride (2.16g; 10mmol) and diisopropylethylamine (4.35ml; 25mmol) was dissolved in DCM (60ml) and cooled under nitrogen on a ice/water bath. Methanesulfonyl chloride (1.56ml; 10.1mmol) was dissolved in DCM (5ml) and added droppwise during 2 min. The reaction mixture was stirred for 2.5 h on the ice/water bath. The reaction mixture was washed with dilute HCl (aq), pH=2, H_2O, and 1M Na_2CO_3. The organic phase was dried (Na_2SO_4), filtered and evaporated to give a crude product that

was recrystallised from THF/n-Heptane. The colourless crystalls was removed by filtration and dried under vaccum at 45°C.

Obtained 1.96g (76% yield) of the title compound.

LC-MS (APCI) m/z 258 (MH+).

^{1}H NMR(DMSO-d_6): δ 7.31 (m, 2H), 7.12 (m, 2H), 3.67 (m, 2H), 2.80 (dt, 2H), 2.64 (m, 1H), 1.85 (m, 2H), 1.65 (m, 2H).

5-Chloro-2-(1-methanesulfonyl-piperidine-4-yloxy)-pyridine

The title compound was prepared as described in the synthesis of 4-(4-Fluoro-phenyl)-1-methanesulfonyl-piperidine.

5-Chloro-2-(piperidine-4-yloxy)-pyridine (2.13g; 10mmol) (preparation of this compound was made as described in WO 99-GB2801), diisopropylethylamine (2.20ml; 12.5mmol) and Methanesulfonyl chloride (1.56ml; 10.1mmol) gave 2.14g (74%) of the title compound.

LC-MS (APCI) m/z 291 (MH+).

^{1}H NMR (DMSO-d_6): δ 8.20 (d, 1H), 7.81 (dd, 1H), 6.87 (d, 1H), 5.09 (m, 1H), 3.41-3.30 (m, 2H), 3.15-3.06 (m, 2H), 2.90 (s, 3H), 2.04 (m, 2H), 1.75 (m, 2H).

1-(methylsulfonyl)-4-[5-(trifluoromethyl)pyridin-2-yl]piperazine

1-[5-(Trifluoromethyl)-Pyridin-2-yl]-piperazine (1.0g; 4.3mmol) and Diisopropylethylamine (0.9ml; 5.4mmol) was dissolved in DCM (10ml). Molecular sieves (4A) was added and the solution was cooled on a ice/water bath. Methanesulfonylchloride (0.9ml; 12mmol) was added and a slurry formed that was stirred for 15 min, the reaction mixture was allowed to reach room temperature and after 1 h. the reaction was quenched by adding 5% $KHCO_3$. Evaporation of solvents and the residue was dissolved between DCM and 5% $KHCO_3$. Separation and extraction of the waterphase with DCM (1x). The combined organic phases was dried ($MgSO_4$), filtered and evaporated to give a crude product as a slightly yellow solid.

Recrystallised (3x) from EtOAc/Heptan gave the title compound as colourless crystalls.

Obtained 1.06g (79% yield) of the title compound.

Purity >95% (HPLC, 254nm)

LC-MS (APCI) m/z 310 (MH+).

^{1}H-NMR(DMSO-d_6): δ 8.44 (1H, bs), 7.85 (1H, dd), 7.02 (1H, d), 3.77 (4H, bt), 3.20 (4H, bt), 2.90 (3H, s).

The following compounds were prepared as described in the synthesis of 1-(methylsulfonyl)-4-[5-(trifluoromethyl)pyridin-2-yl]piperazine

6-[4-(methylsulfonyl)piperazine-1-yl]pyridine-3-carbonitrile

6-(1-Piperazino)-pyridine-3-carbonitrile (2.07g; 11mmol), Diisopropylethylamine (2.4ml; 13.8mmol) and Methanesulfonylchloride (0.86ml; 11mmol) in DCM (20ml) gave 2.53g (86%) of the title compound.

Purity >95% (NMR).

LC-MS (APCI) m/z 267 (MH+).

^{1}H-NMR(DMSO-d_6): δ 8.52 (1H,dd), 7.90 (1H, dd), 7.00 (1H, d), 3.79 (4H, brt), 3.19 (4H, bt), 2.90 (3H, s).

1-(4-fluorophenyl)-4-(methylsulfonyl)piperazine

1-(4-Fluorophenyl)-piperazine (1.98g; 11mmol), Diisopropylethylamine (2.4ml; 13.8mmol) and Methanesulfonylchloride (0.86ml; 11mmol) in DCM (20ml) gave 2.46g (86%) of the title compound.

Purity >95% (NMR).

LC-MS (APCI) m/z 259 (MH+).

^{1}H-NMR(DMSO-d_6): δ 7.11-6.96 (4H, m), 3.28-3.20 (4H, m), 3.20-3.14 (4H, m), 2.92 (3H, s).

1-[(4-fluorophenyl)methyl]-4-(methylsulfonyl)piperazine

1-(4-Fluor-benzyl)-piperazine (2.14g; 11mmol), Diisopropylethylamine (2.4ml; 13.8mmol) and Methanesulfonylchloride (0.86ml; 11mmol) in DCM (20ml) gave 1.97g (65%) of the title compound.

Purity >95% (NMR)

LC-MS (APCI) m/z 273 (MH+).

^{1}H-NMR(DMSO-d_6): δ 7.40-7.28 (2H, m), 7.21-7.10 (2H, m), 3.50 (2H, bs), 3.10 (4H, m), 2.87 (3H, bs), 2.44 (4H, m).

2-[4-(methylsulfonyl)piperazin-1-yl)pyrimidine

1-(2-Pyrimidyl)-piperazine dihydrochloride (2.61g; 11mmol) and Diisopropylethylamine (7.2ml; 41.3mmol) was stirred in DCM (20ml) for 30 min. The precipitated salts was removed by filtration and solvents evaporated, residue was redissolved in DCM (20ml). Diisopropylethylamine (2.4ml; 11mmol) and 4A mol. sieves was added, the yellow solution was cooled on ice/water bath and Methanesulfonylchloride (0.86ml; 11mmol) was added. The resulting red solution was stirred for 15 min, the reaction mixture was allowed to reach room temperature and after 1 h. the reaction was quenched by adding 5% $KHCO_3$. Evaporation of solvents and the residue was dissolved between DCM and 5%$KHCO_3$. Separation difficult due to foam formation. Waterphase was saturated with NaCl and pH adjusted to 10-11. Extraction with EtOAc (3x). The combined organic phases was dried (K_2CO_3), filtered and evaporated to give a crude product as a red solid.

Recrystallised (3x) from EtOAc/Heptan gave the title compound as a red powder.

Obtained 0.6g (22%) of the title compound.

Purity >95% (NMR).

LC-MS (APCI) m/z 243 (MH+).

^{1}H-NMR(DMSO-d_6): δ 8.39 (2H, d), 6.68 (1H, t), 3.85 (4H, bt), 3.17 (4H, bt), 2.88 (3H, s).

4-(4-chlorophenyl)-1-(methylsulfonyl)piperidine

The title compound was prepared as described in the synthesis of 4-(4-Fluoro-phenyl)-1-methanesulfonyl-piperidine.

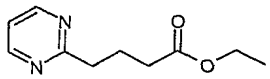
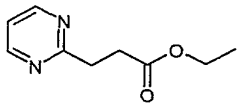
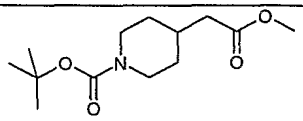
4-(4-Chlorophenyl)piperidine hydrochloride (0.9g, 3.9 mmol), diisopropylethylamine (1.7 ml, 9.7 mmol) and methanesulfonylchloride (0.33ml, 4.3 mmol) in DCM (30ml) and gave 0.82g (78%) of the title compound after recrystallisation from EtOAc/ Heptane.

Purity > 95%.

LC-MS(APCI) m/z 274 (MH+).

^{1}H NMR $CDCl_3$: δ 1.83 (2H, dd); 1.92-2.01 (2H, m); 2.55-2.68 (1H, m); 2.79 (2H, dt); 2.85 (3H, s); 3.97 (2H, d); 7.16 (2H, d); 7.32 (2H, d).

ESTER INTERMEDIATES

Structure	Analysis
	m/z 195 (MH+) ^{1}H-NMR
	m/z 181 (MH+)
	m/z 158 (MH+ - boc)

All other esters used are commercially available or earlier described.

4-Pyrimidin-2-yl-butyric acid ethyl ester

2-Bromopyrimidine (1.0g, 6.3mmol) was slurried in dry THF (8mL). N_2 (g) was bubbled through the slurry for 5 min. $Pd(CH_3CN)_2Cl_2$ (8mg, 0.03mmol) and PPh_3 (23.6mg, 0.09mmol) was added. Under N_2-atmosphere 4-Ethoxy-4-oxo-butylzincbromide (0.5M/THF) (15mL, 7.5mL) was added in one portion. The resulting brown solution was

stirred at room temperature for 2h. H_2O (5mL) was added and the mixture stirred for 60 min. before evaporation of solvents. The residue was redissolved in DCM (150mL) and washed with 0.5M trisodiumcitrate (100mL), H_2O (100mL) and brine (100mL), dried ($MgSO_4$), filtered and evaporated to give 1.3 g of an orange oil. The crude product was purified on 70g of Si-60 gel using a gradient of 100%Heptane to 100% EtOAc as eluent. The fractions containing the product was collected and solvent evaporated to give a yellow oil. Purity by NMR>95% was considered enough for our need. Obtained 1.12g (92% yield) of the title compound.

LC-MS (APCI) m/z 195 (MH+).

^{1}H-NMR($CDCl_3$): δ 8.67 (d, 2H), 7.14 (t, 1H), 4.12 (q, 2H), 3.02 (t, 2H), 2.41 (t, 2H), 2.18 (q, 2H), 1.25 (t, 3H).

3-Pyrimidin-2-yl-propionic acid ethyl ester

2-Bromopyrimidine (1.0g, 6.3mmol) was dissolved in THF (8 mL) and bubbled through with nitrogen. $Pd(MeCN)_2Cl_2$ (8mg, 0.03mmol) and PPh_3 (23.6mg, 0.09mmol) was added followed by addition of 3-ethoxy-3-oxopropylzinkbromid (15mL, 7.5mmol). The reaction was stirred at rt for several days. The crude product was purified on silica with Heptane - EtOAc 3 :1 as eluent giving 0.60g (52%) of the title compound.

LC-MS (APCI) m/z 181 (MH+).

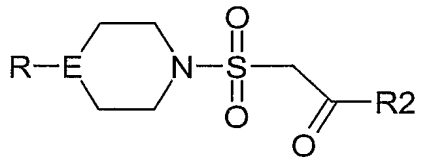
***tert*-butyl 4-(2-methoxy-2-oxoethyl)piperidine-1-carboxylate**

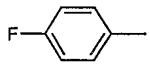
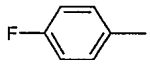
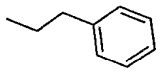
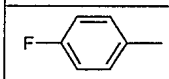
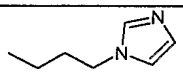
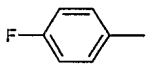
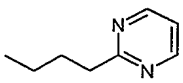
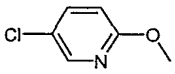
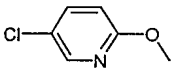
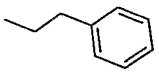
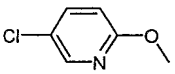
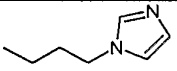
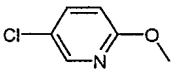
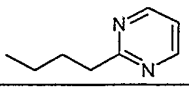
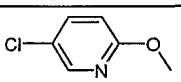
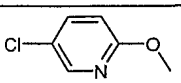
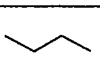
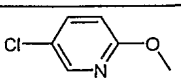
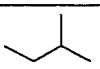
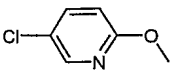
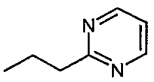
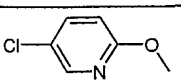
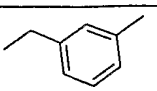
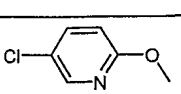
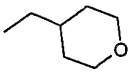
tert-Butyl 4-(2-methoxy-2-oxoethylidene)piperidine-1-carboxylate (3.6 g,14 mmol) and 10% Pd/C moistered with water (0.8 g) was mixed in MeOH (75 mL) and stirred under H_2 (1 atm) for 4 h. The mixture was filtered through Celite and concentrated to give the title compound (3.6 g, 99%).

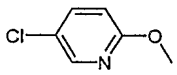
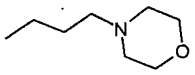
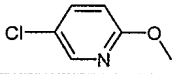
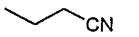
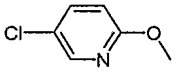
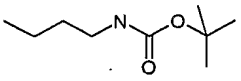
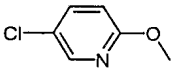
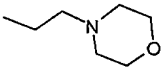
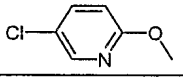
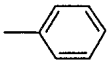
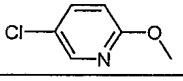
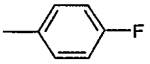
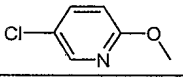
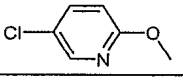
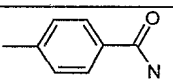
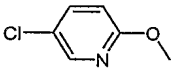
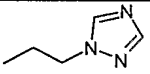
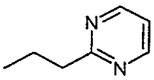
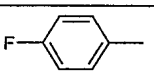
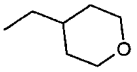
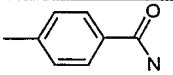
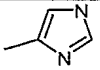
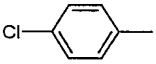
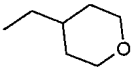
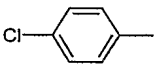
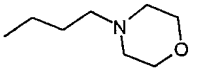
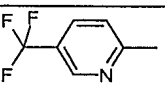
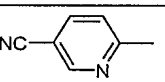
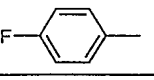
LC-MS (APCI) m/z 158 (MH+-boc).

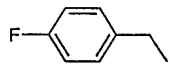
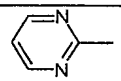
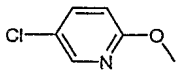
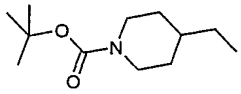
^{1}H NMR ($CDCl_3$): δ 4.07 (2 H, bs); 3.68 (3 H, s); 2.72 (2 H, t); 2.25 (2 H, d, J=7.1 Hz); 2.01-1.86 (1 H, m); 1.68 (2 H, d); 1.46 (9 H, s); 1.23-1.08 (2 H, m).

KETONE INTERMEDIATES



R	E	R2	Analysis
	CH	Me	m/z 300 (MH+)
	CH		H-NMR. see exp. part.
	CH		m/z 394 (MH+)
	CH		m/z 406 (MH+) (1)
	CH	Me	m/z 333 (MH+) (1)
	CH		m/z 423 (MH+)(1)
	CH		m/z 427 (MH+) (1)
	CH		m/z 439 (MH+)(1)
	CH		m/z 347 (MH+)(1)
	CH		m/z 361 (MH+)(1)
	CH		m/z 375 (MH+)(1)
	CH		m/z 425 (MH+)(1)
	CH		m/z 423 (MH+)(1)
	CH		m/z 417 (MH+)(1)

R	E	R2	Analysis
	CH		m/z 446 (MH+)[1]
	CH		m/z 372 (MH+)[1]
	CH		m/z 476 (MH+)[1]
	CH		m/z 432 (MH+)[1]
	CH		m/z 395 (MH+)[1]
	CH		m/z 413 (MH+)[1]
	CH		m/z 385 (MH+)[1]
	CH		-
	CH		m/z 414 (MH+)[1]
	CH		m/z 392 (MH+)[1]
	CH		m/z 384 (MH+)[1]
	CH		m/z 405 (MH+)[1]
	CH		m/z 352 (MH+)[1]
	CH		m/z 400 (MH+)[1]
	CH		m/z 429 (MH+)[1]
	N	Me	m/z 352 (MH+)[1]
	N	Me	m/z 309 (MH+)[1]
	N	Me	m/z 301 (MH+)[1]

R	E	R2	Analysis
	N	Me	m/z 315 (MH+)[1]
	N	Me	m/z 285 (MH+)[1]
	CH		m/z 517 (MH+)[1]

[1] : crude products, no NMR available, mtrl. used directly in next synthetic step.

1-[4-4(Fluoro-phenyl)-piperidine-1-sulfonyl]-propan-2-one.

4-(4-Fluoro-phenyl)-1-methanesulfonyl-piperidine (100mg; 0.39mmol) was dissolved in dry THF (3mL) under a protective nitrogen atmosphere. Lithium bis(trimethylsilyl)amide as a 1.0 M solution in THF (1.0mL; 1.0mmol) was added in one portion at room temperature, the resulting yellow solution was stirred for 45 min. Methylacetate (50mg; 0.68mmol) dissolved in dry THF (0.5mL) was added, the mixture was stirred at room temperature for 40 min. The reaction was quenched by adding NH_4Cl (sat.) (2mL). The mixture was evaporated and the resulting solid was dissolved in a mixture of DCM and H_2O. The organic phase was separated and washed with brine, dried ($MgSO_4$), filtrated and evaporated. The crude product was purified on 20g of Si-60 gel using a gradient of 100%Heptane to 50%EtOAc, a flow of 20mL/min was used and UV=254nm was used for detection. The fractions containing the product was evaporated and this gave the title compound as a colourless solid.

Obtained 70mg (59% yield).

TLC(Si-60; EtOAc:Heptane (2:1)): R_f=0.65

LC-MS (APCI) m/z 300.1 (MH+).

^{1}H-NMR($CDCl_3$): δ 7.17 (m, 2H), 7.01 (m, 2H), 4.02 (s, 2H), 3.93 (m, 2H), 2.94 (dt, 2H), 2.63 (m, 1H), 2.46 (s, 3H), 1.91 (m, 2H), 1.77 (m, 2H).

The following compounds were prepared as described in the synthesis of 1-[4-4(Fluoro-phenyl)-piperidine-1-sulfonyl]-propan-2-one.

1-[4-4(Fluoro-phenyl)-piperidine-1-sulfonyl]-4-phenyl-butan-2-one

4-(4-Fluoro-phenyl)-1-methanesulfonyl-piperidine (100mg; 0.39mmol), Methyl-3-phenylpropionate (112mg; 0.68mmol) and Lithium bis(trimethylsilyl)amide 1.0 M/THF (1.0mL; 1.0mmol) gave 93 mg (61%) of the title compound.

TLC(Si-60; EtOAc:Heptane (2:1)): R_f=0.68

^{1}H-NMR($CDCl_3$): δ 7.30-7.10 (m, 7H), 6.99 (m, 2H), 3.97 (s, 2H), 3.79 (m, 2H), 3.11 (t, 2H), 2.94 (t, 2H), 2.83 (dt, 2H) 2.57 (m, 1H), 1.83 (m, 2H), 1.70 (m, 2H).

1-[4-4(Fluoro-phenyl)-piperidine-1-sulfonyl]-5-imidazol-pentan-2-one

4-(4-Fluoro-phenyl)-1-methanesulfonyl-piperidine (100mg; 0.39mmol), 4-imidazol-1yl-butyric acid ethyl ester (127mg; 0.70mmol) and Lithium bis(trimethylsilyl)amide 1.0 M/THF (1.0mL; 1.0mmol) gave 75 mg (48%) of the title compound.

LC-MS (APCI) m/z 394 (MH+).

^{1}H-NMR($CDCl_3$): δ 7.48 (s, 1H), 7.16 (m, 2H), 7.08 (s, 1H), 7.02 (m, 2H), 6.93 (s, 2H), 4.00 (t, 2H), 3.97 (s, 2H), 3.90 (m, 2H), 2.92 (dt, 2H), 2.77 (t, 2H), 2.63 (m, 1H), 2.12 (q, 2H), 1.92 (m, 2H), 1.77 (m, 2H).

1-[4-(4-Fluoro-phenyl)-piperidine-1-sulfonyl]-5-pyrimidin-2-yl-pentan-2-one

4-(4-Fluoro-phenyl)-1-methanesulfonyl-piperidine (150mg; 0.39mmol) was dissolved in dry THF (3mL) and cooled on an ice/brine mixture. Lithium bis(trimethylsilyl)amide as a 1.0 M solution in THF (1.5mL; 1.5mmol) was added and the mixture was stirred for 40 min. 4-Pyrimidin-2-yl-butyric acid ethyl ester (169mg; 0.87mmol) in THF (0.5mL) was added, the reaction was stirred for 30 min and then allowed to reach room temperature. After 2 h. LC/MS analysis of the reaction mixture showed >98% conversion of the starting material and the reaction was quenched by adding saturated NH_4Cl (aq) (2mL). The mixture was evaporated and the resulting solid was dissolved in a mixture of DCM and

5%$KHCO_3$. The organic phase was separated and the water phase was extracted once with DCM. The combined organic phases was washed with brine, dried ($MgSO_4$), filtered, and evaporated to give a yellow oil. The oil was dissolved in EtOAc and isoHexane was added until a solid formed. Evaporation of solvent gave a yellow solid crude product. This material was analysed using LC/MS only and used without further purification in the next step.

Obtained 234 mg of the crude title compound.

LC-MS (APCI) m/z 406.1 (MH+).

The following compounds were prepared as described in the synthesis of 1-[4-(4-Fluoro-phenyl)-piperidine-1-sulfonyl]-5-pyrimidin-2-yl-pentan-2-one. They were obtained as crude products and used without further purification.

1-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonyl]-propan-2-one

Starting from 5-Chloro-2-(1-methanesulfonyl-piperidine-4-yloxy)-pyridine (150mg; 0.51mmol), Methylacetate (61mg; 0.82mmol) and Lithium bis(trimethylsilyl)amide 1.0M/THF (1.3ml; 1.3mmol).

Obtained 161mg of the crude title compound. Used without further purification.

LC-MS (APCI) m/z 333.1 (MH+).

1-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonyl]-4-phenyl-butan-2-one

Starting from 5-Chloro-2-(1-methanesulfonyl-piperidine-4-yloxy)-pyridine (150mg; 0.51mmol), Methyl-3-phenylpropionate (126mg; 0.77mmol) and Lithium bis(trimethylsilyl)amide 1.0 M/THF (1.3ml; 1.3mmol).

Obtained 258mg of the crude title compound. Used without further purification.

LC-MS (APCI) m/z 423.2 (MH+).

1-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonyl]-5-imidazol-1-yl-pentan-2-one

Starting from 5-Chloro-2-(1-methanesulfonyl-piperidine-4-yloxy)-pyridine (150mg; 0.51mmol), 4-imidazol-1yl-butyric acid ethyl ester (140mg; 0.77mmol) and Lithium bis(trimethylsilyl)amide 1.0 M/THF (1.3ml; 1.3mmol).

Obtained 268mg of the crude title compound. Used without further purification.

LC-MS (APCI) m/z 427.2 (MH+).

1-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonyl]-5-pyrimidin-2-yl-pentan-2-one

Starting from 5-Chloro-2-(1-methanesulfonyl-piperidine-4-yloxy)-pyridine (150mg; 0.51mmol), 4-Pyrimidin-2-yl-butyric acid ethyl ester (147mg; 0.76mmol) and Lithium bis(trimethylsilyl)amide 1.0 M/THF (1.3ml; 1.3mmol).

Obtained 244mg of the crude title compound. Used without further purification.

LC-MS (APCI) m/z 439.2 (MH+).

1-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonyl]-butan-2-one

LC-MS (APCI) m/z 347 (MH+)

1-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonyl]-pentan-2-one

LC-MS (APCI) m/z 361 (MH+)

1-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonyl]-4-methyl-pentan-2-one

LC-MS (APCI) m/z 375 (MH+)

1-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonyl]-4-pyrimidin-2-yl-butan-2-one

LC-MS (APCI) m/z 425 (MH+)

1-({4-[(5-Chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)-3-(3-methylphenyl)propan-2-one

LC-MS (APCI) m/z 423 (MH+)

1-({4-[(5-Chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)-3-tetrahydro-2H-pyran-4-ylpropan-2-one

LC-MS (APCI) m/z 417 (MH+)

1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)-5-morpholin-4-ylpentan-2-one

LC-MS (APCI) m/z 446 (MH+)

5-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)-4-oxopentanenitrile

LC-MS (APCI) m/z 372 (MH+)

1,1-dimethylethyl 5-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)-4-oxopentylcarbamate

LC-MS (APCI) m/z 476 (MH+)

1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)-4-morpholin-4-ylbutan-2-one

LC-MS (APCI) m/z 432 (MH+)

2-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)-1-phenylethanone

LC-MS (APCI) m/z 395 (MH+)

2-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)-1-(4-fluorophenyl)ethanone

LC-MS (APCI) m/z 413 (MH+)

2-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)-1-(1H-imidazol-4-yl)ethanone

LC-MS (APCI) m/z 385 (MH+)

4-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)acetyl]benzamide

n.d.

1-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)-4-(1H-1,2,4-triazol-1-yl)butan-2-one

LC-MS (APCI) m/z 414 (MH+)

1-{[4-(4-fluorophenyl)piperidin-1-yl]sulfonyl}-4-pyrimidin-2-ylbutan-2-one

LC-MS (APCI) m/z 392 (MH+)

1-{[4-(4-fluorophenyl)piperidin-1-yl]sulfonyl}-3-tetrahydro-2H-pyran-4-ylpropan-2-one

LC-MS (APCI) m/z 384 (MH+)

4-({[4-(4-fluorophenyl)piperidin-1-yl]sulfonyl}acetyl)benzamide

LC-MS (APCI) m/z 405 (MH+)

2-{[4-(4-fluorophenyl)piperidin-1-yl]sulfonyl}-1-(1H-imidazol-4-yl)ethanone

LC-MS (APCI) m/z 352 (MH+)

1-{[4-(4-chlorophenyl)piperidin-1-yl]sulfonyl}-3-tetrahydro-2H-pyran-4-ylpropan-2-one

LC-MS (APCI) m/z 400 (MH+)

1-{[4-(4-chlorophenyl)piperidin-1-yl]sulfonyl}-5-morpholin-4-ylpentan-2-one

LC-MS (APCI) m/z 429 (MH+)

1-({4-[5-(trifluoromethyl)pyridin-2-yl]piperazine-1-yl}sulfonyl)propan-2-one
LC-MS (APCI) m/z 352.1 (MH+)

6-{4-[(2-oxopropyl)sulfonyl]piperazin-1-yl}pyridine-3-carbonitrile
LC-MS (APCI) m/z 309.1 (MH+)

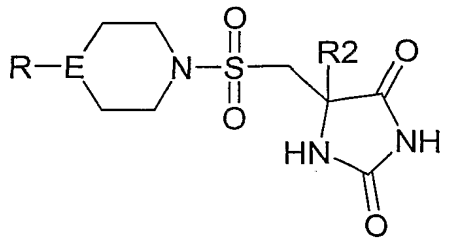
1-{[4-(4-fluorophenyl)piperazine-1-yl]sulfonyl}propan-2-one
LC-MS (APCI) m/z 301.1 (MH+)

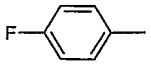
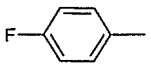
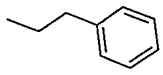
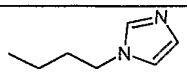
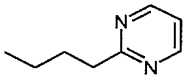
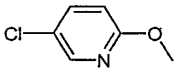
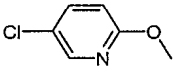
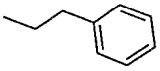
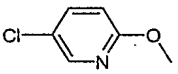
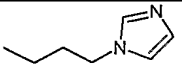
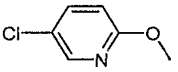
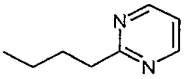
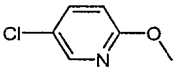
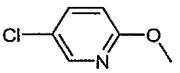
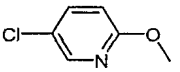
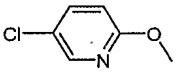
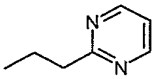
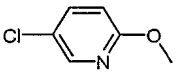
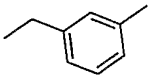
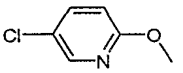
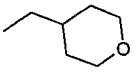
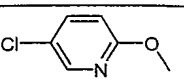
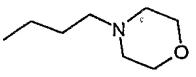
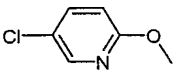
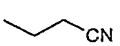
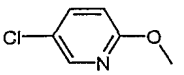
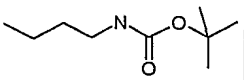
1-({4-[(4-fluorophenyl)methyl]piperazine-1-yl}sulfonyl)propan-2-one
LC-MS (APCI) m/z 315.1 (MH+)

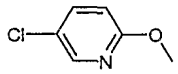
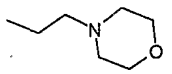
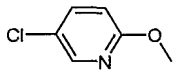
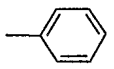
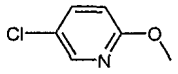
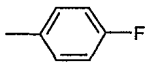
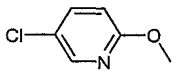
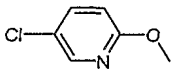
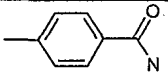
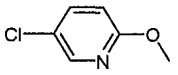
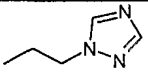
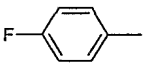
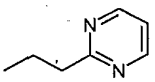
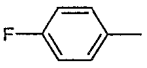
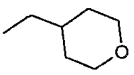
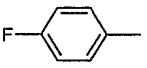
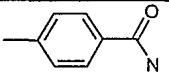
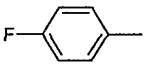
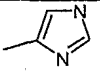
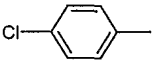
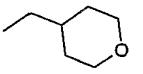
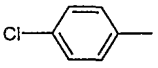
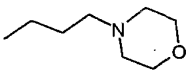
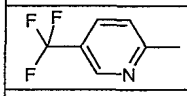
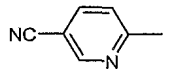
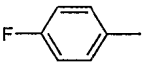
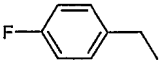
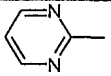
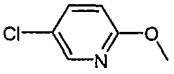
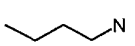
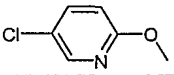
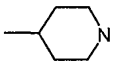
1-[(4-pyrimidin-2-ylpiperazine-1-yl)sulfonyl]propan-2-one
LC-MS (APCI) m/z 285.1 (MH+)

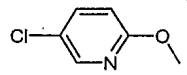
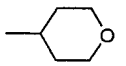
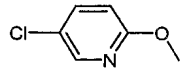
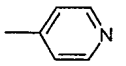
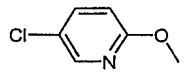
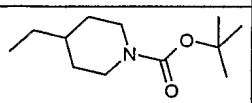
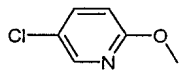
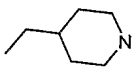
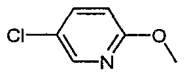
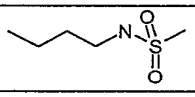
1,1-dimethylethyl 4-[3-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)-2-oxopropyl]piperidine-1-carboxylate
LC-MS (APCI) m/z 517 (MH+).

HYDANTOINS OF FORMULA II



R	E	R2	Analysis
	CH	Me	m/z 370 (MH+)[1]
	CH		m/z 460 (MH+)[1]
	CH		m/z 464 (MH+)[1]
	CH		m/z 476 (MH+)[1]
	CH	Me	m/z 403 (MH+)[1]
	CH		m/z 493 (MH+)[1]
	CH		m/z 497 (MH+)[1]
	CH		m/z 509 (MH+)[1]
	CH		m/z 417 (MH+)[1]
	CH		m/z 431 (MH+)[1]
	CH		m/z 445 (MH+)[1]
	CH		m/z 495 (MH+)[1]
	CH		m/z 493 (MH+)[1]
	CH		m/z 487 (MH+)[1]
	CH		m/z 517 (MH+)[1]
	CH		m/z 442 (MH+)[1]
	CH		m/z 547, 490 (MH+), -tBu[1]

R	E	R2	Analysis
	CH		m/z 502 (MH+)[2]
	CH		m/z 465 (MH+)[2]
	CH		m/z 483 (MH+)[2]
	CH		m/z 455 (MH+)[2]
	CH		m/z 508 (MH+)[2]
	CH		m/z 484 (MH+)[2]
	CH		m/z 462 (MH+)[1]
	CH		m/z 454 (MH+)[1]
	CH		m/z 475 (MH+)[1]
	CH		m/z 422 (MH+)[2]
	CH		m/z 470 (MH+)[1]
	CH		m/z 499 (MH+)[1]
	N	Me	m/z 422 (MH+)[1]
	N	Me	m/z 379 (MH+)[1]
	N	Me	m/z 371 (MH+)[1]
	N	Me	m/z 385 (MH+)[1]
	N	Me	m/z 355 (MH+)[1]
	CH		m/z 446 (MH+)[1]
	CH		m/z 472 (MH+)[1]

R	E	R2	Analysis
	CH		m/z 4o3 (MH+)[1]
	CH		m/z 466 (MH+)[1]
	CH		m/z 530 (MH+ - boc)[1]
	CH		m/z 486 (MH+ - boc)[1]
	CH		m/z 524 (MH+)[1]

[1] : NMR available, see experimental part.

[2] : Not purified.

(5R,S)-5-[4-(4-Fluoro-phenyl)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

The ketone 1-[4-4(Fluorophenyl)-piperidine-1-sulfonyl]-propan-2-one (68mg; 0.23mmol), KCN (30mg; 0.46mmol) and $(NH_4)_2CO_3$ (111mg; 1.16mmol) was suspended in 50% EtOH/H_2O (8mL) in a 22 mL sealed tube and heated to 70°C, a solution was formed. The mixture was stirred at 70°C for 17 h. a solid formed in the tube, the mixture was cooled to room temperature and solvent evaporated, the residue was suspended in water and pH adjusted to pH=6 using 1.0M HCl and preciptated product removed by filtration and washed with water. The water phase was saturated with NaCl and extracted with MeCN. The solid material and MeCN solutions was combined and evaporated. The crude product was purified using a semipreparative HPLC system and a C-18 column with MeCN/H_2O+0.1%TFA as eluent. Fractions containing the product was combined and solvent removed by evaporation to give the title compound as a colourless solid.

Obtained 53 mg (62% yield).

Purity by NMR >98%

LC-MS (APCI) m/z 370.0 (MH+).

^{1}H-NMR (DMSO-d_6): δ 10.74 (s, 1H), 8.02 (s, 1H), 7.31 (m, 2H), 7.12 (m, 2H), 3.61 (m, 2H), 3.51 (d, 1H), 3.34 (d, 1H), 2.86 (m, 2H), 2.63 (m, 1H), 1.82 (m, 2H), 1.63 (m, 2H), 1.34 (s, 3H).

(5R,S)-5-[4-(4-Fluoro-phenyl)-piperidine-1-sulfonylmethyl]-5-phenethyl-imidazolidine-2,4-dione

The title compound was prepared as described in the synthesis of (5R,S)-5-[4-(4-Fluoro-phenyl)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione.

1-[4-4(Fluorophenyl)-piperidine-1-sulfonyl]-4-phenyl-butan-2-one (93mg; 0.24mmol), KCN (40mg; 0.61mmol) and $(NH_4)_2CO_3$ (117mg; 1.22mmol) gave 37mg (33%) of the title compound.

LC-MS (APCI) m/z 460.1 (MH+).

^{1}H-NMR (DMSO-d_6): δ 10.87 (s, 1H), 8.13 (s, 1H), 7.30 (m, 4H), 7.15 (m, 5H), 3.63 (m, 2H), 3.56 (d, 1H), 3.41 (d, 1H), 2.87 (m, 2H), 2.61 (m, 2H), 2.39 (m, 1H), 1.92 (bt, 2H), 1.83 (m, 2H), 1.63 (m, 2H).

(5R,S)-5-[4-(4-Fluoro-phenyl)-piperidine-1-sulfonylmethyl]-5-(3-imidazol-1-yl-propyl)-imidazolidine-2,4-dione

1-[4-4(Fluorophenyl)-piperidine-1-sulfonyl]-5-imidazol-butan-2-one (75mg; 0.19mmol), KCN (30mg; 0.46mmol) and $(NH_4)_2CO_3$ (91mg; 0.95mmol) was dissolved in EtOH/H_2O (1/1) (10mL) in a sealed 22 mL tube and stirred for 17.5 h at 70 °C. Another portion of KCN (40mg; 0.61mmol) and $(NH_4)CO_3$ (250mg; 2.60 mmol) was added and the mixture was stirred at 70 °C for another 16 h. Evaporation of solvent and the residual material was suspended in H_2O, precipitating crude product was removed by filtration and purified using a semipreparative HPLC system and a C-18 column with MeCN/H_2O+0.1%TFA as eluent. Fractions containing the product was combined and MeCN was removed by evaporation, the acidic waterphase was made basic, pH=8-9, using 5% $KHCO_3$ and the precipitating product was extracted using EtOAc. Organic phase dried (Na_2SO_4), filtered and evaporated to give the title compound as a colourless solid.

Obtained 60mg (68% yield)

LC-MS (APCI) m/z 464.2 (MH+).

^{1}H-NMR (DMSO-d_6): δ 10.75 (bs, 1H), 8.06 (s, 1H), 7.59 (s, 1H), 7.30 (m, 2H), 7.16-7.08 (m, 3H), 6.88 (s, 1H), 3.95 (m, 2H), 3.60 (m, 2H), 3.47 (d, 1H), 3.35 (d, 1H), 2.86 (m, 2H), 2.62 (m, 1H), 1.86-1.50 (m, 8H).

(5R,S)-5-[4-(4-Fluoro-phenyl)-piperidine-1-sulfonylmethyl]-5-(3-pyrimidin-2-yl-propyl)-imidazolidine-2,4-dione

Crude 1-[4-(4-Fluoro-phenyl)-piperidine-1-sulfonyl]-5-pyrimidin-2-yl-pentan-2-one (234mg; max 0.58mmol), KCN (151mg; 2.3mmol) and $(NH_4)_2CO_3$ (557mg; 5.8mmol) was suspended in EtOH/H_2O (1/1) (26mL) in a 40mL sealed tube. The mixture was heated 70°C and the resulting yellow solution was stirred for 16h.

LC/MS analysis showed that 15% unreacted ketone remained and another portion of KCN (65mg; 1mmol) and $(NH_4)_2CO_3$ (245mg; 2.55mmol) was added and the mixture was heated to 70°C for another 16h. Solvent was removed by evaporation and the residue was treated with H_2O (25mL). The precipitating crude product was removed by filtration and purified using semipreparative HPLC system and a C-18 column with MeCN/H_2O+0.1%TFA as eluent. Fractions containing the product was combined and MeCN was removed by evaporation, the acidic waterphase was made basic, pH=8-9, using 5% $KHCO_3$ and the precipitating product was filtered off, washed with water and dried in a desiccator under reduced pressure at 40°C over night. This gave the title compound as a colourless solid. Purity >98% by NMR.

Obtained 120mg (43% yield, 2 steps).

LC-MS (APCI) m/z 476.2 (MH+).

^{1}H-NMR (DMSO-d_6): δ 10.77 (s, 1H), 8.72 (d, 2H), 8.03 (s, 1H), 7.36-7.27 (m, 3H), 7.15-7.09 (m, 2H), 3.60 (m, 2H), 3.50 (d, 1H), 3.34 (d, 1H), 2.92-2.80 (m, 4H), 2.62 (m, 1H), 1.86-1.54 (m, 8H).

The following compounds were prepared as described in the synthesis of (5R,S)-5-[4-(4-Fluoro-phenyl)-piperidine-1-sulfonylmethyl]-5-(3-pyrimidin-2-yl-propyl)-imidazolidine-2,4-dione.

(5R,S)-5-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

Purification not needed, after evaporation of reaction mixture and addition of water the precipitating product was pure enough >98% by HPLC (220nm, 254nm) and NMR. Obtained 147mg (71% yield, 2steps) of the title compound as a colorless solid.

LC-MS (APCI) m/z 403.1 (MH+).

^{1}H-NMR (DMSO-d_6): δ 10.73 (bs, 1H), 8.20 (d, 1H), 8.01 (s, 1H), 7.81 (dd, 1H), 6.87 (d, 1H), 5.09 (m, 1H), 3.52 (d, 1H), 3.35 (d, 1H), 3.42-3.26 (m, 2H + H_2O), 3.18-3.06 (m, 2H), 2.08-1.96 (m, 2H), 1.79-1.65 (m, 2H), 1.33 (s, 3H).

(5S)-5-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione and **(5R)-5-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione**

The coresponding racemic material (74mg), was dissolved in 36mL of isoHexane/EtOH (25/75) and separated into the pure enantiomers by using the following Gilson HPLC system:

Column: CHIRALCEL OD, 2.0x25 cm, flow = 6.0 mL/min, eluent = isoHexane/EtOH (25/75), temp = ambient, detector UV = 220nm.

The enantiomers were collected and analysed on a CHIRALCEL OD-H, 0.46x25 cm, 0.5 mL/min, isoHexane/EtOH (25/75), ambient temperature, 220nm.

Rt = 9.88 min. ee>99% for the faster eluting enantiomer, 29mg (39%).

Rt = 11.45 min. ee=98.7% for the slower eluting enatiomer, 27mg (36%).

LC-MS (APCI) m/z 403.1 (MH+).

(5R,S)-5-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-5-phenethyl-imidazolidine-2,4-dione.

Starting from crude 1-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonyl]-4-phenyl-butan-2-one (258mg; max 0.51mmol).

Purification of crude product was made on 70g Si-60 gel using DCM+5%MeOH as eluent.

Purity >96% by NMR and HPLC (220nm, 254nm).

Obtained 201mg (80% yield, 2 steps) of the title compound as a colourless solid.

LC-MS (APCI) m/z 493.0 (MH+).

^{1}H-NMR (DMSO-d_6): δ 10.86 (bs, 1H), 8.21 (bd, 1H), 8.13 (s, 1H), 7.81 (dd, 1H), 7.33-7.24 (m, 2H), 7.22-7.14 (m, 3H), 6.87 (d, 1H), 5.10 (m, 1H), 3.56 (d, 1H), 3.42 (d, 1H), 3.43-3.28 (m, 2H + H_2O), 3.20-3.08 (m, 2H), 2.66-2.52 (m, 1H), 2.45-2.31 (m, 1H), 2.08-1.96 (m, 2H), 1.96-1.83 (m, 2H), 1.81-1.65 (m, 2H.

(5R,S)-5-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-5-(3-imidazol-1yl-propyl)-imidazolidine-2,4-dione

Starting from crude 1-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonyl]-5-imidazol-1-yl-pentan-2-one (268mg; max 0.51mmol).

Obtained 151mg (59% yield, 2 steps) of the title compound as a colourless solid.

Purity >98% by NMR.

LC-MS (APCI) m/z 497.2 (MH+).

^{1}H-NMR (DMSO-d_6): δ 10.81 (bs, 1H), 8.20 (d, 1H), 8.05 (s, 1H), 7.81 (dd, 1H), 7.59 (bs, 1H), 7.13 (bs, 1H), 6.88 (bs, 1H), 6.87 (d, 1H), 5.08 (m, 1H), 3.47 (d, 1H), 3.40-3.28 (m, 3H + H_2O), 3.17-3.06 (m, 2H), 2.07-1.95 (m, 2H), 1.79-1.64 (m, 3H), 1.61-1.48 (m, 3H).

(5R,S)-5-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-5-(3-pyrimidin-2-yl-propyl)-imidazolidine-2,4-dione

Starting from crude 1-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonyl]-5-pyrimidin-2-yl-pentan-2-one (244mg; max 0.51mmol).

Obtained 105mg (49% yield, 2 steps) of the title compound as a colourless solid.

Purity >98% by NMR.

^{1}H-NMR (DMSO-d_6): δ 10.77 (bs, 1H), 8.72 (d, 2H), 8.20 (d, 1H), 8.03 (s, 1H), 7.81 (dd, 1H), 7.34 (t, 1H), 6.87 (d, 1H), 5.08 (m, 1H), 3.50 (d, 1H), 3.41-3.29 (m, 3H + H_2O), 3.16-3.07 (m, 2H), 2.83 (t, 2H), 2.06-1.96 (m, 2H), 1.81-1.66 (m, 5H), 1.63-1.51 (m, 1H).

(5S)-5-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-5-(3-pyrimidin-2-yl-propyl)-imidazolidine-2,4-dione and **(5R)-5-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-5-(3-pyrimidin-2-yl-propyl)-imidazolidine-2,4-dione**

The coresponding racemic material (40mg), was dissolved in 26mL of isoHexane/EtOH (25/75) and separated into the pure enantiomers by using the same conditions as described for separation of (5R,S)-5-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione.

Rt = 17.6 min. ee>99% for the faster eluting enantiomer, 17mg (42%).

Rt = 21.0 min. ee=98.9% for the slower eluting enatiomer, 15mg (37%).

LC-MS (APCI) m/z 509 (MH+).

5-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-5-ethylimidazolidine-2,4-dione

LC-MS (APCI) m/z 417 (MH+).

^{1}H NMR (DMSO-d_6): δ 0.76 (3H, t); 1.63 (2H, q); 1.66-1.76 (2H, m); 1.96-2.06 (2H, m); 3.12 (2H, bt); 3.48, 3.35 (1H each, ABq, *J*=14.9); 3.32-3.41 (2H, m); 5.04-5.12 (1H, m); 6.86 (1H, d); 7.80 (1H, dd); 7.96 (1H, s); 8.19 (1H, d); 10.73 (1H, s).

LC-MS (APCI) m/z 417 (MH+).

5-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-5-propylimidazolidine-2,4-dione

LC-MS (APCI) m/z 431 (MH+).

^{1}H NMR (DMSO-d_6): δ 0.84 (3H, t); 1.03-1.16 (1H, m); 1.20-1.35 (1H, m); 1.58 (2H, t); 1.65-1.77 (2H, m); 1.96-2.06 (2H, m); 3.11 (2H, t); 3.21-3.42 (3H, D_2O); 3.48 (1H, half

ABq, *J*=14.9); 5.04-5.12 (1H, m); 6.86 (1H, d); 7.80 (1H, dd); 7.99 (1H, s); 8.19 (1H, d); 10.74 (1H, s).

5-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-5-(2-methylpropyl)imidazolidine-2,4-dione

LC-MS (APCI) m/z 445 (MH+).

^{1}H NMR (DMSO-d_6): δ 0.81 (3H, d); 0.88 (3H, d); 1.50-1.59 (3H, m); 1.64-1.78 (2H, m); 1.95-2.05 (2H, m); 3.06-3.16 (2H, m); 3.22-3.41 (3H, D_2O); 3.46 (1H half Abq, *J*=15.1); 5.03-5.12 (1H, m); 6.86 (1H, d); 7.80 (1H, dd); 7.99 (1H, bs); 8.19 (1H, d); 10.71 (1H, bs).

5-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-5-(2-pyrimidin-2-ylethyl)imidazolidine-2,4-dione

LC-MS (APCI) m/z 495 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.66-1.78 (2H, m); 1.96-2.16 (4H, m); 2.64-2.76 (1H, m); 2.84-2.95 (1H, m); 3.08-3.18 (2H, m); 3.33-3.41 (2H, m); 3.43, 3.57 (1H each, ABq, *J*=14.9); 5.04-5.12 (1H, m); 6.86 (1H, d); 7.34 (1 H, t); 7.80 (1H, dd); 8.12 (1H, d); 8.19 (1H, d); 8.70 (1H, d); 10.84 (1H, s).

5-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-5-[(3-methylphenyl)methyl]imidazolidine-2,4-dione

LC-MS (APCI) m/z 493 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.66-1.78 (2H, m); 1.96-2.07 (2H, m); 2.23 (3H, s); 2.84 (2H, s); 3.09-3.20 (2H, m); 3.34-3.43 (2H, m); 3.45, 3.69 (1H each, ABq, *J*=14.7 Hz); 5.06-5.13 (1H, m); 6.87 (1H, d); 6.93-6.98 (2H, m); 7.01-7.06 (1H, m); 7.10-7.17 (1H, m); 7.81 (1H, dd); 8.08 (1H, s); 8.20 (1H, d); 10.35 (1H, s).

5-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-5-(tetrahydro-2H-pyran-4-ylmethyl)imidazolidine-2,4-dione

LC-MS (APCI) m/z 487 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.06-1.26 (2H, m); 1.39-1.77 (7H, m); 1.95-2.05 (2H, m); 3.06-3.27 (4H, m); 3.27-3.41 (3H, D_2O); 3.48 (1H half ABq, *J*=15.0 Hz); 3.69-3.79 (2H, m); 5.03-5.12 (1H, m); 6.85 (1H, d); 7.80 (1H, dd); 8.03 (1H, bs); 8.19 (1H, d); 10.79 (1H, s).

5-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-5-(3-morpholin-4-ylpropyl)imidazolidine-2,4-dione trifluoroacetic acid

LC-MS (APCI) m/z 517 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.40-1.78 (6H, m); 1.96-2.06 (2H, m); 2.94-3.18 (6H, m); 3.31-3.44 (5H, m); 3.54 (1H half Abq, *J*=14.9 Hz); 3.60 (2H, t); 3.90-4.01 (2H, m); 4.25-6.27 (1H);6.85 (1H, d); 7.80 (1H, dd); 8.05 (1H, bs); 8.19 (1H, d); 9.52 (1H, bs); 10.88 (1H, s).

3-{4-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-2,5-dioxoimidazolidin-4-yl}propanenitrile

LC-MS (APCI) m/z 442 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.66-1.78 (2H, m); 1.95-2.05 (4H, m); 2.37-2.57 (2H, DMSO-d_6); 3.07-3.17 (2H, m); 3.25-3.40 (2H, D_2O); 3.42, 3.52 (1H each, Abq, *J*=14.7); 5.04-5.12 (1H, m); 6.86 (1H, d); 7.80 (1H, dd); 7.99 (1H, bs); 8.20 (1H, d); 10.91 (1H, s).

1,1-dimethylethyl 3-{4-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-2,5-dioxoimidazolidin-4-yl}propylcarbamate

LC-MS (APCI) m/z 547, 490 (MH+); (MH+)-tBu.

^{1}H NMR (DMSO-d_6): δ 1.10-1.27 (1H, m); 1.27-1.43 (9H, s); 1.52-1.77 (4H, m); 1.94-2.06 (2H, m); 2.80-2.90 (2H, m); 3.06-3.16 (2H, m); 3.22-3.40 (4H, D_2O); 3.47 (1H half ABq, *J*=15.1 Hz); 5.03-5.12 (1H, m); 6.76-6.88 (2H, m); 7.80 (1H, dd); 7.95 (1H, bs); 8.19 (1H, d); 10.73 (1H, bs).

5-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-5-(2-morpholin-4-ylethyl)imidazolidine-2,4-dione

Not purified.

LC-MS (APCI) m/z 502 (MH+).

5-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-5-phenylimidazolidine-2,4-dione

Not purified.

LC-MS (APCI) m/z 465 (MH+).

5-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-5-(4-fluorophenyl)imidazolidine-2,4-dione

Not purified.

LC-MS (APCI) m/z 483 (MH+).

5-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-5-(1H-imidazol-4-yl)imidazolidine-2,4-dione

Not purified.

LC-MS (APCI) m/z 455 (MH+).

4-{4-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-2,5-dioxoimidazolidin-4-yl}benzamide

Not purified.

LC-MS (APCI) m/z 508 (MH+).

5-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-5-[2-(1H-1,2,4-triazol-1-yl)ethyl]imidazolidine-2,4-dione

Not purified.

LC-MS (APCI) m/z 484 (MH+).

5-({[4-(4-fluorophenyl)piperidin-1-yl]sulfonyl}methyl)-5-(2-pyrimidin-2-ylethyl)imidazolidine-2,4-dione

LC-MS (APCI) m/z 462 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.62 (2H, dq); 1.77-1.86 (2H, m); 2.07-2.19 (2H, m); 2.57-2.76 (2H, m); 2.81-2.96 (3H, m); 3.42, 3.56 (1H each, ABq, *J*=14.6 Hz); 3.59-3.68 (2H, m); 7.11 (2H, t); 7.27-7.36 (3H, m); 8.08 (1H, bs); 8.71 (1H, d); 10.84 (1H, bs).

5-({[4-(4-fluorophenyl)piperidin-1-yl]sulfonyl}methyl)-5-(tetrahydro-2H-pyran-4-ylmethyl)imidazolidine-2,4-dione

LC-MS (APCI) m/z 454 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.07-1.28 (2H, m); 1.40-1.68 (7H, m); 1.77-1.85 (2H, m); 2.56-2.67 (1H, m); 2.85 (2H, dq); 3.22 (2H, dq); 3.39-3.45 (1H, m); 3.48 (1H half ABq, *J*=14.5 Hz); 3.53-3.66 (2H, m); 3.75 (2H, dt); 7.11 (2H, t); 7.26-7.33 (2H, m); 8.00 (1H, bs); 10.68 (1H, bs).

4-[4-({[4-(4-fluorophenyl)piperidin-1-yl]sulfonyl}methyl)-2,5-dioxoimidazolidin-4-yl]benzamide

LC-MS (APCI) m/z 475 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.61 (2H, dq); 1.77-1.88 (2H, m); 2.58-2.69 (1H, m); 2.85-3.01 (2H, m); 3.60 (1H half ABq, *J*=14.6 Hz); 3.60-3.69 (2H, m); 7.12 (2H, t); 7.26-7.34 (2H, m); 7.42 (1H, bs); 7.65 (2H, d); 7.91 (2H, d); 8.01 (1H, bs); 8.85 (1H, s); 10.95 (1H, bs).

5-({[4-(4-fluorophenyl)piperidin-1-yl]sulfonyl}methyl)-5-(1H-imidazol-4-yl)imidazolidine-2,4-dione

Not purified.

LC-MS (APCI) m/z 422 (MH+).

5-({[4-(4-chlorophenyl)piperidin-1-yl]sulfonyl}methyl)-5-(tetrahydro-2H-pyran-4-ylmethyl)imidazolidine-2,4-dione

LC-MS (APCI) m/z 470 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.07-1.28 (2H, m); 1.40-1.68 (7H, m); 1.76-1.85 (2H, m); 2.56-2.68 (1H, m); 2.85 (2H, q); 3.22 (2H, q); 3.48 (1H half ABq, *J*=14.5 Hz); 3.53-3.67 (2H, m); 3.75 (2H, t); 7.26-7.37 (4H, m); 8.02 (1H, bs); 10.79 (1H, bs).

5-({[4-(4-chlorophenyl)piperidin-1-yl]sulfonyl}methyl)-5-(3-morpholin-4-ylpropyl)imidazolidine-2,4-dione trifluoroacetic acid

LC-MS (APCI) m/z 499 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.41-1.87 (8H, m); 2.56-2.69 (1H, m); 2.86 (2H, q); 2.95-3.14 (4H, m); 3.33-3.44 (3H, m); 3.52 (1H half ABq, *J*=14.6 Hz); 3.55-3.69 (4H, m); 3.90-4.00 (2H, m); 7.25-7.37 (4H, m); 8.07 (1H, s); 9.89 (1H, bs); 10.87 (1H, s).

(5R,S)-5-Methyl-5-[({4-[5-(trifluoromethyl)pyridin-2-yl]piperazine-1-yl}sulfonyl)methyl]imidazolidine-2,4-dione

LC-MS (APCI) m/z 422.1 (MH+).

Purity >95% by NMR.

^{1}H-NMR (DMSO-d_6): δ 10.75 (1H, s); 8.44 (1H, d); 8.02 (1H, s); 7.85 (1H, dd); 7.03 (1H, d); 3.75 (4H, m); 3.55 (1H, d); 3.35 (1H, d); 3.21 (4H, m); 1.31 (3H, s).

6-(4-{[({4R,S}-4-methyl-2,5-dioxoimidazolidin-4-yl)methyl]sulfonyl}piperazin-1-yl)pyridine-3-carbonitril

LC-MS (APCI) m/z 379.1 (MH+).

Purity >99% by NMR.

^{1}H-NMR (DMSO-d_6): δ 10.74 (1H, s); 8.52 (1H, d); 8.00 (1H, s); 7.90 (1H, dd); 7.00 (1H, d); 3.78 (4H, m); 3.55 (1H, d); 3.36 (1H, d); 3.20 (4H, m); 1.31 (3H, s).

(5R,S)-5-({[4-(4-fluorophenyl)piperazine-1-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione

LC-MS (APCI) m/z 371.1 (MH+).

Purity >98% by NMR.

^{1}H-NMR (DMSO-d_6): δ 10.75 (1H, s); 8.03 (1H, s); 7.11-6.95 (4H, m); 3.56 (1H, d); 3.36 (1H, d); 3.25 (4H, m); 3.15 (4H, m); 1.33 (3H, s).

(5R,S)-5-[({4-[(4-fluorophenyl)methyl]piperazine-1-yl}sulfonyl)methyl]-5-methylimidazolidine-2,4-dione

LC-MS (APCI) m/z 385.1 (MH+).

Purity >95% by NMR.

^{1}H-NMR (DMSO-d_6): δ 10.72 (1H, s); 7.99 (1H, s); 7.33 (2H, m); 7.15 (2H, m); 3.50 (2H, s); 3.49 (1H, d); 3.30 (1H, d); 3.12 (4H, m); 2.42 (4H, m); 1.32 (3H, s).

(5R,S)-5-methyl-5-{[(4-pyrimidin-2-ylpiperazine-1-yl)sulfonyl]methyl}imidazolidine-2,4-dione.

LC-MS (APCI) m/z 355.1 (MH+).

Purity >99% by NMR.

^{1}H-NMR (DMSO-d_6): δ 10.74 (1H, s); 8.40 (2H, d); 8.01 (1H, s); 6.68 (1H, t); 3.83 (4H, m); 3.53 (1H, d); 3.33 (1H, d); 3.18 (4H, m); 1.31 (3H, s).

5-(3-aminopropyl)-5-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]imidazolidine-2,4-dione trifluoroacetic acid

1,1-dimethylethyl 3-{4-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-2,5-dioxoimidazolidin-4-yl}propylcarbamate (426mg, 0.78mmol) was dissolved in 10 mL CH_2Cl_2 and 4 mL of TFA was added. The reaction was stirred at rt for 1 hour. The solvent was removed to give 408mg (93%) of the title compound as a white solid.

LC-MS (APCI) m/z 446 (MH+).

^{1}H NMR (CD_3OD): δ 1.48-1.63 (1H, m); 1.69-1.96 (5H, m); 2.01-2.12 (2H, m); 2.93 (2H,

t); 3.20-3.29 (2H, m); 3.40, 3.60 (1H each ABq, *J*=14.6 Hz); 3.44-3.54 (2H, m); 4.85 (4H, D_2O); 5.14-5.22 (1H, m); 6.78 (1H, d); 7.67 (1H, dd); 8.08 (1H, d).

5-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-5-piperidin-4-yl-imidazolidine-2,4-dion hydro chloride

4-{4-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-2,5-dioxo-imidazolidin-4-yl}-piperidine-1-carboxylic acid *tert*-butyl ester (100 mg, 0.16 mmol) was solved in 2 M hydrogen chloride (ethyl acetate, 30 ml) and methanol (5 ml). The solution was stirred at 50 °C for 1 hour. Evaporation afforded 90.5 mg (0.16 mmol) of the title compound 5-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-5-piperidin-4-yl-imidazolidine-2,4-dion hydro chloride in quantitative yield.

LC-MS (APCI) m/z 472.3 (MH+).

^{1}H NMR (DMSO-d_6): δ10.88 (1H, s); 9.05 (1H, d); 8.48 (1H,m); 8.21 (1H, d); 7.82 (1H, dd); 6.87 1H, d); 5.10 1H, m); 3.47 (2H, s); 3.43-3.13 (7H, m); 2.78 (2H, m); 2.02-1.39 (9H, m).

4-{4-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-2,5-dioxo-imidazolidin-4-yl}-piperidine-1-carboxylic acid *tert*-butyl ester

For preparation of the reacting ester, piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-methyl ester, se for example Albert A Carr et al, Journal of Organic Chemistry (1990), 55(4), 1399-401.

LC-MS (APCI) m/z 472.3 (MH+-Boc).

5-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-5-(tetrahydo-pyran-4-yl)-2,4-dion

LC-MS (APCI) m/z 403.2 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.77 (1H,s); 8.20 (1H, d); 8.19 (1H,s); 7.81 (1H, dd); 6.87 (1H, d); 5.09 (1H, m); 3.88 (2H, t); 3.45 (2H, s); 3.38 (2H, m); 3.21 (2H, t); 3.13 (2H, m); 2.02 (2H, m); 1.84 (1H, t); 1.72 (2H, m); 1.60 (1H, d); 1.32 (4H, m).

5-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-5-pyridin-4-yl-imidazolidine-2,4-dion trifluoroacetic acid

LC-MS (APCI) m/z 466.2 (MH+).

^{1}H NMR (DMSO-d_6): δ 11.15 (1H, s); 8.97 (1H, s); 8.76 (2H, d); 8.20 (1H, d); 7.82 (2H, dd); 7.80 (1H, d); 6.86 (1H, d); 5.10 (1H, m); 4.17 (1H, m); 3.73 (1H, d); 3.41 (2H, m); 3.17 (2H, m); 2.08 (2H, m); 1.72 (2H, m).

1,1-dimethylethyl 4-({4-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-2,5-dioxoimidazolidin-4-yl}methyl)piperidine-1-carboxylate

The title compound was prepared essentially as described in the synthesis of (5R,S)-5-[4-(4-Fluoro-phenyl)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine- 2,4-dione

LC-MS (APCI) m/z 530 (MH+ -boc).

^{1}H NMR (DMSO-d_6): δ 0.88-1.10 (2H, m); 1.30-1.77 (16H, m); 1.94-2.06 (2H, m); 2.53-2.77 (2H, m); 3.05-3.17 (2H, m); 3.21-3.41 (4H, D_2O); 3.48 (1H half ABq, *J*=14.7 Hz); 3.73-3.88 (2H, m); 5.03-5.12 (1H, m); 6.86 (1H, d); 7.80 (1H, dd); 8.04 (1H, bs); 8.19 (1H, d); 10.55 (1H, bs).

5-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-5-(piperidin-4-ylmethyl)imidazolidine-2,4-dione trifluoroacetate

The title compound was prepared as described in the synthesis of 5-(3-aminopropyl)-5-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]imidazolidine-2,4-dione trifluoroacetic acid.

LC-MS (APCI) m/z 486 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.17-1.40 (2H, m); 1.47-1.81 (7H, m); 1.94-2.07 (2H, m); 2.75-2.93 (2H, m); 3.06-3.42 (7H, m); 3.50 (1H half ABq, *J*=15.6 Hz); 5.04-5.12 (1H, m); 6.85 (1H, d); 7.80 (1H, dd); 8.06 (1H, s); 8.08-8.22 (2H, m); 8.45 (1H, bd); 10.85 (1H, s).

N-(3-{4-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-2,5-dioxoimidazolidin-4-yl}propyl)methanesulfonamide

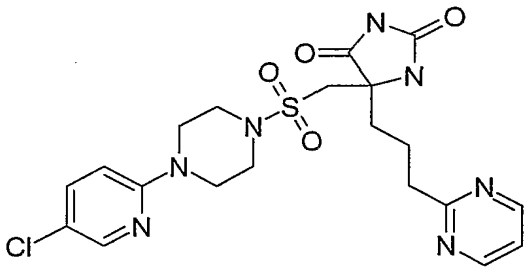
5-(3-Aminopropyl)-5-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]imidazolidine-2,4-dione trifluoroacetic acid (100mg, 0.18mmol) was slurried in 2 mL DCM. DIPEA (62μL, 0.36mmol) was added and the slurry was stirred for some minutes. Sulfonylchloride (16μL, 0.18mmol) was added and the reaction was stirred at rt over night. The crude product was purified by preparative HPLC.

LC-MS (APCI) m/z 524 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.19-1.52 (2H, m); 1.58-1.77 (4H, m); 1.95-2.06 (2H, m); 2.85 (3H, s); 2.83-2.93 (2H, m); 3.12 (2H, t); 3.19-3.46 (3H, D_2O); 3.50 (1H half ABq, *J*=15.7 Hz); 5.04-5.12 (1H, m); 6.86 (1H, d); 6.97 (1H, t); 7.80 (1H, dd); 8.01 (1H, s); 8.19 (1H, d); 10.79 (1H, s).

EXAMPLE 14

(5R,S)-5-[4-(5-Chloro-pyridin-2-yl)-piperazine-1-sulfonylmethyl]-5-(3-pyrimidin-2-yl-propyl)-imidazolidine-2,4-dione



1-([4-(5-Chloro-2-pyridinyl)-1-piperazinyl]sulfonyl)-5-(2-pyrimidinyl)-2-pentanone (0.397 g, 0.936 mmol), potassium cyanide (0.122 g, 1.87 mmol), ammonium carbonate (0.500 g, 4.68 mmol) and 50% ethanol (4 mL) were stirred in a sealed vial at 75°C (oil temp) for 17 hours. The ethanol was removed by rotary evaporation, pH was adjusted to 6 with 1M HCl, the suspension was filtered, the solid was washed with a little water,

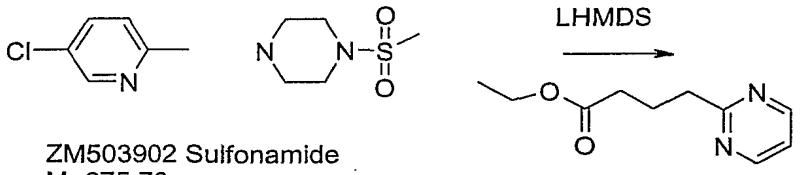
collected and dried in vacuo at 45°C. Some more product was recovered from the aqueous filtrate by adding solid sodium chloride to saturation and extracting the mixture with acetonitrile (2x10 mL). Drying with Na_2SO_4, filtering and concentrating the organic phase gave a second crop. The combined crops were dissolved in tetrahydrofuran (5-10 mL), adsorbed on silica (3 g) and applied on a short silica column. Elution with EtOAc followed by EtOAc-MeCN (1:1) gave 0.30 g (65% yield) of the title compound as a white crystalline solid.

LC-MS (APCI) m/z 494 (MH+).

^{1}H NMR (DMSO-d_6) δ 10.78 (1H, bs); 8.70 (2H, d, *J*= 5Hz); 8.13 (1H, d, *J*= 3Hz); 8.02 (1H, s); 7.63 (1H, dd, J_1= 3Hz, J_2= 9Hz); 7.33 (1H, t, *J*= 5Hz); 6.93 (1H, d, *J*= 10Hz); 3.63-3.56 (4H, m); 3.52 (1H, d, *J*= 14Hz); 3.34 (1H, d, *J*= 14Hz; obscured by water signal), 3.24-3.14 (4H, m); 2.82 (2H, t, *J*= 7Hz) and 1.79-1.50 (4H,m's). ^{13}C NMR (DMSO-d_6) δ 175.6, 169.5, 157.2, 157.0, 156.5, 145.6, 137.3, 119.2, 119.1, 108.8, 62.4, 52.7, 44.5, 38.2, 36.4 and 21.2.

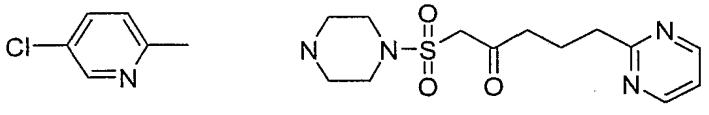
The starting materials were prepared as follows:

1-([4-(5-Chloro-2-pyridinyl)-1-piperazinyl]sulfonyl)-5-(2-pyrimidinyl)-2-pentanone



ZM503902 Sulfonamide
M=275.76

ZM503902 Ester
M=194.23



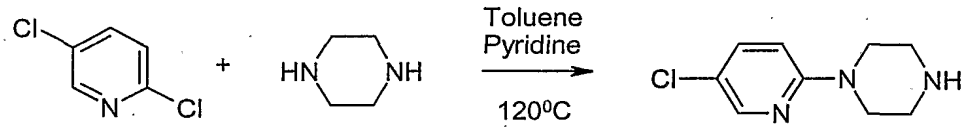
ZM503902 Ketone
M=423.93

A stirred solution of 1-(5-Chloro-2-pyridinyl)-1-methylsulfonyl piperazine (0.64g, 2.32mmol) in dry THF (25 mL, 40 rel vol), under nitrogen, was cooled to -10°C causing the sulfonamide to precipitate out of solution. LHMDS 1M in THF (4.64mL, 4.64mmol) was added dropwise, over 4 min, to the suspension of sulfonamide, the mixture was then stirred for 40 min. 4-(2-Pyrimidinyl)-butyric acid ethyl ester (0.68g, 3.48mmol) (example 8) in dry THF (6.4 mL, 10 rel vol) was added dropwise, over 4 min, and the mixture stirred for 30 min. The mixture was quenched with saturated NH_4Cl (0.64 mL, 1 rel vol) and evaporated to a semi-solid residue. The residue was taken up in DCM (20 rel vol) and the organic layer was washed with water (15 mL, 24 rel vol), brine (15mL, 24 rel vol), and dried with $MgSO_4$. Removal of the solvent by rotary evaporation gave the crude product as an off white solid (0.84g, 85%). The crude product was purified by Biotage FLASH chromatography, using ethyl acetate/isohexane (90:10) as eluant, to give pure ketone as a white amorphous solid.

1-(5-Chloro-2-pyridinyl)-1-methylsulfonyl piperazine

To a solution containing 1-(5-Chloro-2-pyridinyl)-piperazine (1 eq.) in toluene (25 volumes) is added triethylamine (1.1eq), and the mixture is cooled down to 5°C in an ice bath. Methanesulfonyl chloride diluted with toluene (0.5vols) is slowly added to the cooled solution, keeping the temperature below 10°C. Once the addition is finished, the reaction is allowed to warm-up to room temperature. Water (6.6vols) is added and the mixture is filtered and cake slurried in Toluene (2 vols). The cake is then washed with Toluene (2 vols) and dried in a vacuum oven at 40°C overnight.

1-(5-Chloro-2-pyridinyl)-piperazine



DCP Piperazine ZM503902 Pyridine

M.W. 148 M.W. 86 M.W. 197.5

Piperazine (4 eq) is charged in the reaction vessel as a solid. At room temperature pyridine (1.43 vols) is added to the vessel followed by toluene (2.14 vols). The final slurry is stirred and heated to reflux at 120°C to obtain a complete solution. To a separate vessel charge 2,5-dichloropyridine (DCP) followed by Toluene (1.43 vols) to dissolve the solid. The dissolution is endothermic, and it is necessary to warm up the solution to ~ 30°C to get complete solution. The solution containing DCP is then slowly discharged into the reaction vessel over 5hours. At this point the remaining amount of DCP should be about 20%. The reaction is left refluxing overnight to reach completion.

The reaction mixture is allowed to cool to room temperature, then water is added (6 vols). The two layers are separated, and the aqueous phase is re-extracted with Toluene (5 vols). The two organic layers are combined and re-washed with H_2O (6 vols). Finally, the organic layer is washed with brine (6 vols).

(5S)-5-[4-(5-Chloro-pyridin-2-yl)-piperazine-1-sulfonylmethyl]-5-(3-pyrimidin-2-yl-propyl)-imidazolidine-2,4-dione and **(5R)-5-[4-(5-Chloro-pyridin-2-yl)-piperazine-1-sulfonylmethyl]-5-(3-pyrimidin-2-yl-propyl)-imidazolidine-2,4-dione**

The coresponding racemic material (23mg) was dissolved in 8 mL of isoHexane/EtOH (25/75) and separated into the pure enantiomers by using the following Gilson HPLC system:

Column: CHIRALCEL OD, 2.0x25 cm, flow = 6.0 mL/min, eluent = isoHexane/EtOH (25/75), temp = ambient, detector UV = 230nm.

The enantiomers were collected and analysed on a CHIRALCEL OD-H, 0.46x25 cm, 0.5 mL/min, isoHexane/EtOH (25/75), ambient temperature, 220nm.

Rt = 11.5 min. ee>99% for the faster eluting enantiomer, 8.7mg (37%).

LC-MS (APCI) m/z 494.1 (MH+).

$[\alpha]_D$ = -26.4° (c=0.0022 g/mL, EtOH, t=20°C)

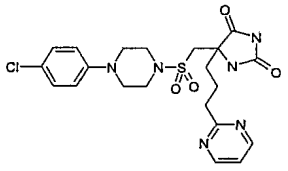
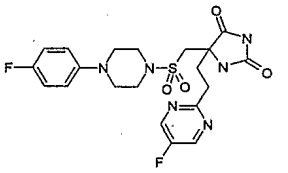
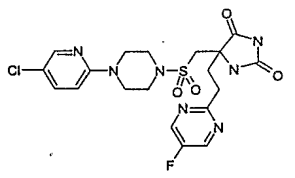
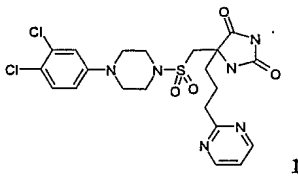
Rt = 14.5 min. ee=98 % for the slower eluting enatiomer, 9mg (39%).

LC-MS (APCI) m/z 494.1 (MH+).

$[\alpha]_D$ = +24.5° (c=0.0026 g/mL, EtOH, t=20°C)

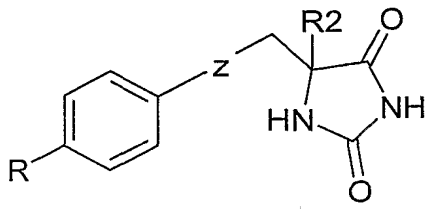
EXAMPLE 15

The following compounds were prepared using a method analogous to that described in Example 13 or 14.

5-[4-(4-Chloro-phenyl)-piperazine-1-sulfonylmethyl]-5-(3-pyrimidin-2-yl-propyl]-imidazolidine-2,4-dione	 m/z 493 (MH+)
5-[4-(4-Fluoro-phenyl)-piperazine-1-sulfonylmethyl]-5-[2-(5-fluoro-pyrimidin-2-yl)-ethyl]-imidazolidine-2,4-dione	 m/z 481 (MH+)
5-[4-(5-Chloro-pyridin-2-yl)-piperazine-1-sulfonylmethyl]-5-[2-(5-fluoro-pyrimidin-2-yl-ethyl]-imidazolidine-2,4-dione	 m/z 498 (MH+)
5-[4-(3,4-Dichloro-phenyl)-piperazine-1-sulfonylmethyl]-5-(3-pyrimidin-2-yl-propyl]-imidazolidine-2,4-dione	 m/z 527 (MH+)

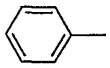
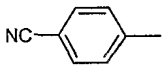
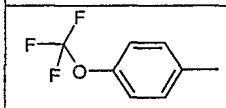
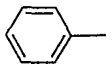
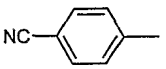
EXAMPLE 16

Compounds with the general formula



were synthesised according to the method described in Example 13.

KETONE INTERMEDIATES

R	R2	z	Analysis (1)
	Me	S	GC/MS m/z 242 (M^+)
	Me	S	GC/MS m/z 267 (M^+)
	Me	S	GC/MS m/z 326 (M^+)
	Me	SO2	LC/MS m/z 275 (MH+)
	Me	SO2	-

(1): For NMR-data see experimental part.

1-(1,1'-biphenyl-4-ylthio)propan-2-one

1-[(4-bromophenyl)thio]propan-2-one (357 mg, 1.46 mmol) was treated with phenyl boronic acid (231 mg, 1.89 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloro palladium (II) complex with dichloromethane (1:1) (36 mg), toluene (20 ml), methanol

(7.5 ml), saturated sodium carbonate solution (3.5 ml) and were stirred together at 80 °C for 18 hours. After cooling the reaction mixture was treated with dilute hydrochloric acid and extracted into ethyl acetate. The product was purified by flash chromatography on silica, eluting with 25 % ethyl acetate : iso-hexane to give 277 mg product.

GC/MS m/z: 242 [M^+].

^{1}H NMR ($CDCl_3$): δ 2.33 (3H, s); 3.73 (2H, s); 7.37 (1H, s); 7.42-7.48 (4H, m); 7.54-7.59 (4H, m).

The following compounds were prepared as described in the synthesis of 1-(1,1'-biphenyl-4-ylthio)propan-2-one

4'-[(2-oxopropyl)thio]-1,1'-biphenyl-4-carbonitrile

GC/MS m/z: 267 [M +].

^{1}H NMR ($CDCl_3$): δ 2.34 (3H, s); 3.75 (2H, s); 7.44, 7.54 (4H, abq, *J*=8.5 Hz); 7.67, 7.74 (4H, abq, *J*=8.5 Hz).

1-({4'-[(trifluoromethyl)oxy]-1,1'-biphenyl-4-yl}thio)propan-2-one

GC/MS m/z: 326 [M +].

^{1}H NMR ($CDCl_3$): δ 2.34 (3H, s); 3.73 (2H, s); 7.30 (2H, d); 7.43 (2H, d); 7.51 (2H, d); 7.58 (2H, d).

1-(1,1'-biphenyl-4-ylsulfonyl)propan-2-one

1-(1,1'-biphenyl-4-ylthio)propan-2-one (69 mg, 0.28mmol) was stirred at room temperature with sodium bicarbonate (72 mg, 0.85 mmol), oxone ((525 mg, 0.85 mmol), water (5 ml) and methanol (10ml) for 3 hours. Water (50 ml) was added and the product extracted into ethyl acetate (3 x 25 ml). The extracts were brine washed, sodium sulphate dried and evaporated to give 78 mg (99%) product that was of sufficient purity to use with out further purification.

LC-MS (APCI) m/z 275 (MH+).

^{1}H NMR ($CDCl_3$): δ 2.47 (3H, s); 4.22 (2H, s); 7.44-7.54 (3H, m); 7.64 (2H, d); 7.80, 7.97 (4H, abq, *J*=8.6 Hz).

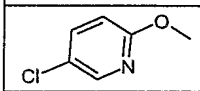
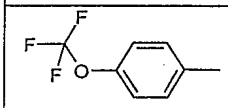
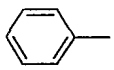
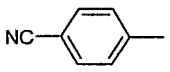
4'-[(2-oxopropyl)sulfonyl]-1,1'-biphenyl-4-carbonitrile

The title compound was prepared as described in the synthesis of 1-(1,1'-biphenyl-4-ylsulfonyl)propan-2-one.

^{1}H NMR (DMSO-d_6): δ 2.48 (3H, s); 4.23 (2H, s); 7.74 (2H, d); 7.81 (4H, t); 8.02 (2H, d).

HYDANTOINS OF FORMULA II

The following compounds were prepared as described in the synthesis of (5R,S)-5-[4-(4-Fluoro-phenyl)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione (Example 13).

R	R2	z	Analysis [(1)]
	Me	SO2	m/z 396 (MH+)
	Me	S(O)	m/z 413 (MH+)
	Me	SO2	m/z 345 (MH+)
	Me	SO2	m/z 370 (MH+)

[(1)]: For NMR-data see experimental part.

(5R,S)-[4-(5-Chloro-pyridin-2-yloxy)-benzenesulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 396 (MH+).

^{1}H NMR (DMSO-d6): δ 1.27 (3H, s); 3.71, 3.78 (1H each, ABq, J=15.0); 7.23 (1H, d); 7.36-7.41 (2H, m); 7.82-7.87 (3H, m); 8.04 (1H, dd); 8.27 (1H, d); 10.79 (1H, s).

5-chloro-2-{[4-(methylsulfonyl)phenyl]oxy}pyridine

2,5-dichloropyridine (1.48g; 10mmol), 4-methylsulfonylphenol (1.89g; 11mmol) and Cs_2CO_3 (4.24g; 13mmol) was slurried in 75mL of NMP. The slurry was heated to approx 170°C over night. After cooling the Cs_2CO_3 was filtered off and the solvent was extracted between H_2O and EtOAc. The organic phase was dried over Na_2SO_4 and evaporated. Heptane:EtOAc 2:1 was added to the residue and the crystalls was filtered off.1.42 g (50%).

LC-MS(APCI) m/z 284 (MH+).

^{1}H NMR $CDCl_3$: δ 3.09 (3H, s); 7.02 (1H, d); 7.33 (2H, d); 7.76 (1H, dd); 8.00 (2H, d); 8.17 (1H, s).

5-methyl-5-[({4'-[(trifluoromethyl)oxy]-1,1'-biphenyl-4-yl}sulfinyl)methyl]imidazolidine-2,4-dione

5-methyl-5-[({4'-[(trifluoromethyl)oxy]-1,1'-biphenyl-4-yl}thio)methyl]imidazolidine-2,4-dione (48 mg, 0.112 mmol) was stirred at room temperature with oxone (50 mg), sodium bicarbonate (50 mg), water (5 ml) and Methanol (10 ml) for 18 hours. The solid was filtered off and crystalissed from ethanol to give 20 mg of the title compound.

LC-MS(APCI) m/z very weak 413 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.41 (3H, s); 3.04-3.27 (2H, m); 7.47 (2H, d); 7.67-7.73 (2H, m); 7.78-7.90 (5H, m); 8.21 and 8.37 (1H, 2 s); 10.79 and 10.91 (1H, 2 s)

5-methyl-5-[({4'-[(trifluoromethyl)oxy]-1,1'-biphenyl-4-yl}thio)methyl]imidazolidine-2,4-dione

LC-MS(APCI) m/z very weak 397 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.33 (3H, s); 3.29 (2H, s); 7.42-7.45 (4H, m); 7.61 (2H, d); 7.77 (2H, d); 7.99 (1H, s); 10.75 (1H, s).

5-[(1,1'-biphenyl-4-ylsulfonyl)methyl]-5-methylimidazolidine-2,4-dione

LC-MS(APCI) m/z 345 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.27 (3H, s); 3.72, 3.81 (2H, abq, *J*=15.3 Hz); 7.45 (1H, t); 7.52 (2H, t); 7.76 (2H, d); 7.82 (1H, s); 7.88, 7.94 (4H, abq, *J*=8.9 Hz); 10.80 (1H, bs).

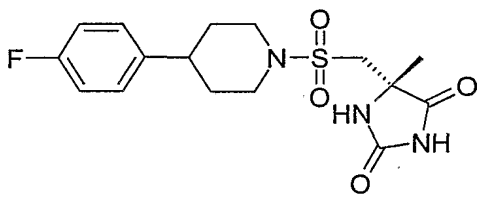
4'-{[(4-methyl-2,5-dioxoimidazolidin-4-yl)methyl]sulfonyl}-1,1'-biphenyl-4-carbonitrile

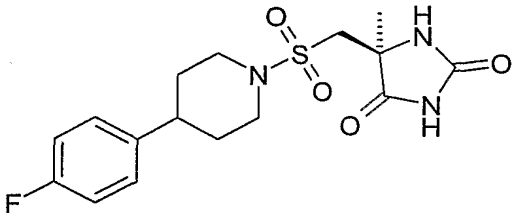
LC-MS(APCI) m/z very weak 370 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.26 (3H, s); 3.74, 3.84 (2H, abq, *J*=16.0 Hz); 7.81 (1H, s); 7.91-8.03 (8H, m); 10.81 (1H, s).

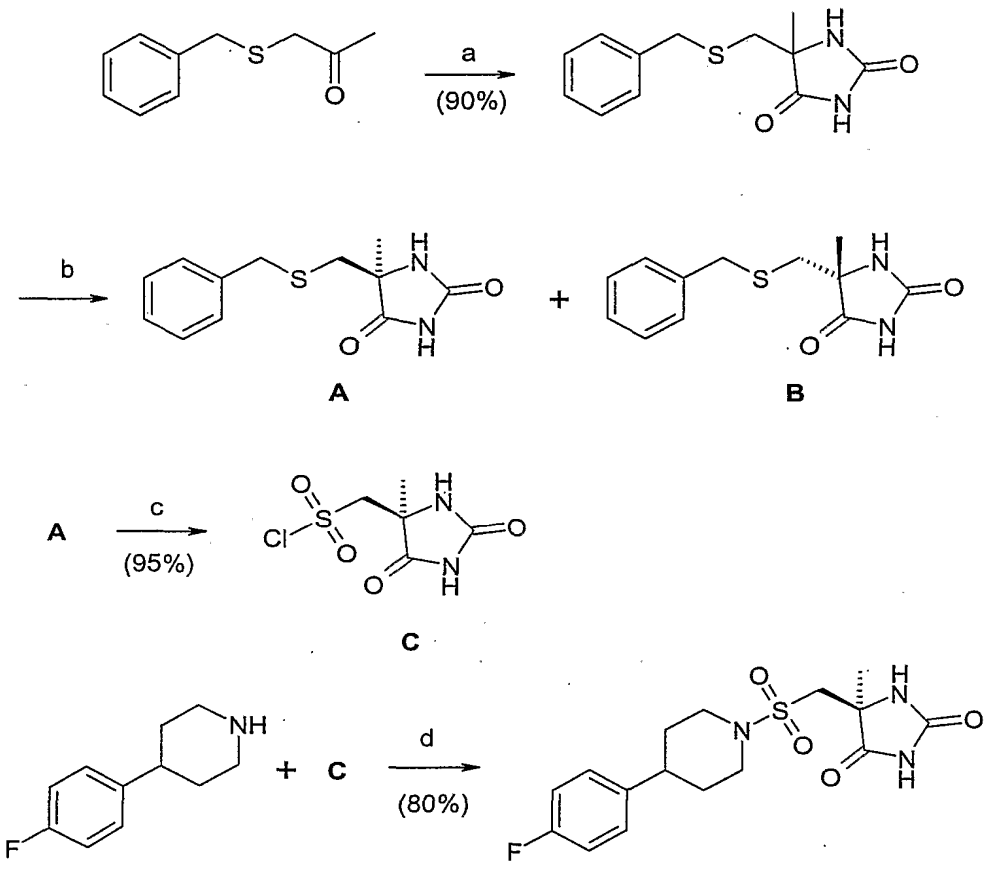
EXAMPLE 17

Synthesis of enantiomeric pure hydantoins





Representative synthetic route is shown overleaf.



Reagents and conditions: a) KCN, NH_4CO_3, $EtOH/H_2O$, +90°C, 3h. b) Chiral separation, CHIRALPAK AD, Methanol as eluent. c) Cl_2 (g), $AcOH/H_2O$, <+15°C, 25min. d) Diisopropylethylamine, THF. -20°C, 30 min.

Experimental procedures

(5*S*)-5-({[4-(4-fluorophenyl)piperidin-1-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione

4-(4-Fluorophenyl)piperidine hydrochloride (63 mg, 0.29 mmol) was taken up in 3 mL of dry THF , neutralized with diisopropylethylamine (50 µL, 0.29 mmol) and cooled on an ice-water bath. [(4*S*)-4-metyl-2,5-dioxo-imidazolodin-4-yl]methanesulfonyl chloride (80 mg, 0.35 mmol) was added and after stirring for 10 min, diisopropylethylamine (50 µL, 0.29 mmol) was added and the reaction mixture was stirred at ambient temperature until LC-MS (APCI) indicated consumption of the amine. The reaction mixture was evaporated

and the residue taken up in EtOH and heated to 50 °C and allowed to cool before water was added. The precipitated product was collected and washed with EtOH/water and dried in vacuum to yield 87 mg.

LC-MS (APCI) m/z 370 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.73 (1 H, s); 8.01 (1 H, s); 7.29 (2 H, dd); 7.11 (2 H, dd); 3.61 (2 H, dd); 3.50, 3.33 (1 H each, ABq, *J*=14.7 Hz); 2.91-2.80 (2 H, m); 2.67-2.57 (1 H, m); 1.82 (2 H, d); 1.62 (2 H, ddd); 1.33 (3 H, s).

The starting materials were prepared as follows:

5-methyl-5-{[(phenylmethyl)thio]methyl}imidazolidine-2,4-dione

A steel vessel was charged with ethanol and water (315mL/135mL).

31.7g (0.175 mol) of benzylthioacetone, 22.9g (0.351 mol) of potassium cyanide and 84.5g (0.879 mol) of ammonium carbonate was added. The closed reaction vessel was kept in an oil bath (bath temperature 90 °C) under vigorous stirring for 3h.

The reaction vessel was cooled with ice-water (0.5 h), the yellowish slurry was evaporated to dryness and the solid residue partitioned between 400 mL water and 700 mL ethylacetate and separated. The water-phase was extracted with ethylacetate (300 mL). The combined organic phases were washed with saturated brine (150 mL), dried (Na_2SO_4), filtered and evaporated to dryness. If the product did not crystallize, 300 mL of dichloromethane was added to the oil. Evaporation gave the product as a slightly yellowish powder,43.8 g (90%).

LC-MS (APCI) m/z 251.1 (MH+).

^{1}H NMR (DMSO-d_6) δ: 10.74 (1H,s); 8.00 (1H, s); 7.35-7.20 (5H, m); 3.76 (2H, s); 2.72, 2.62 (1H each, ABq, *J*=14.0 Hz); 1.29 (3H, s).

^{13}C NMR (DMSO-d_6) δ: 177.30, 156.38, 138.11, 128.74, 128.24, 126.77, 62.93, 37.96, 36.39, 23.15.

(5*S*)-5-methyl-5-{[(phenylmethyl)thio]methyl}imidazolidine-2,4-dione

The title compound was prepared by chiral separation of the racemic material using a 250mm x 50mm column on a Dynamic Axial Compression Preparative HPLC system. The stationary phase used was CHIRALPAK AD, eluent=Methanol, flow=89mL/min, temp=ambient, UV=220nm, sample conc=150mg/mL, injection volume=20mL.

Retention time for title compound = 6 min.

Analysis of chiral purity was made using a 250mm x 4.6mm CHIRALPAK-AD column from Daicel, flow=0.5mL/min, eluent=Ethanol, UV=220nm, temp=ambient.

Retention time for title compound = 9.27min.

Purity estimated to >99% ee.

LC-MS (APCI) m/z 251.1 (MH+).

$[\alpha]_D$=-30.3° (c=0.01g/mL, MeOH, T=20°C).

^{1}H NMR (DMSO-d_6) δ: 10.74 (1H,s); 8.00 (1H, s); 7.35-7.20 (5H, m); 3.76 (2H, s); 2.72, 2.62 (1H each, ABq, *J*=14.0 Hz); 1.29 (3H, s).

^{13}C NMR (DMSO-d_6) δ: 177.30, 156.28, 138.11, 128.74, 128.24, 126.77, 62.93, 37.96, 36.39, 23.15.

(5*R*)-5-methyl-5-{[(phenylmethyl)thio]methyl}imidazolidine-2,4-dione

The title compound was prepared by chiral separation of the racemic material using a 250mm x 50mm column on a Dynamic Axial Compression Preparative HPLC system. The stationary phase used was CHIRALPAK AD, eluent=Methanol, flow=89mL/min, temp=ambient, UV=220nm, sample conc=150mg/mL, injection volume=20mL.

Retention time for title compound = 10 min.

Analysis of chiral purity was made using a 250mm x 4.6mm CHIRALPAK-AD column from Daicel, flow=0.5mL/min, eluent=Ethanol, UV=220nm, temp=ambient.

Retention time for title compound = 17.81 min.

Chiral purity estimated to >99% ee.

LC-MS (APCI) m/z 251.0 (MH+).

$[\alpha]_D$=+30.3° (c=0.01g/mL, MeOH, T=20°C).

^{1}H NMR (DMSO-d_6) δ: 10.74 (1H,s); 8.00 (1H, s); 7.35-7.20 (5H, m); 3.76 (2H, s); 2.72, 2.62 (1H each, ABq, *J*=14.0 Hz); 1.29 (3H, s).

^{13}C NMR (DMSO-d_6) δ: 177.31, 156.30, 138.11, 128.74, 128.25, 126.77, 62.94, 37.97, 36.40, 23.16.

[(4*S*)-4-methyl-2,5-dioxoimidazolidin-4-yl]methanesulfonyl chloride

(5S)-5-methyl-5-{[(phenylmethyl)thio]methyl}imidazolidine-2,4-dione (42.6g; 0.17mol) was dissolved in a mixture of AcOH (450 mL) and H_2O (50 mL). The mixture was immersed in an ice/water bath, Cl_2 (g) was bubbled through the solution, the flow of gas was adjusted so that the temperature was kept below +15 °C. After 25 min the solution became yellow-green in colour and a sample was withdrawn for LC/MS and HPLC analysis. It showed that starting material was consumed. The yellow clear solution was stirred for 30 min and an opaque solution /slurry was formed.

The solvent was removed on a rotary evaporator using waterbath with temperature held at +37°C. The yellowish solid was suspended in Toluene (400mL) and solvent removed on the same rotary evaporator. This was repeated once more.

The crude product was then suspended in iso-Hexane (400mL) and warmed to +40°C while stirring, the slurry was allowed to cool to room temperature before the insoluble product was removed by filtration, washed with iso-Hexane (6x100mL), and dried under reduced preassure at +50°C over night. This gave the product as a slightly yellow powder. Obtained 36.9 g (95%) of the title compound.

Purity by HPLC = 99%, NMR supported that purity.

$[\alpha]_D$=-12.4° (c=0.01g/mL, THF, T=20°C).

^{1}H NMR (THF-d_8): δ 9.91 (1H, bs); 7.57 (1H, s); 4.53, 4.44 (1H each, ABq, *J*=14.6Hz); 1.52 (s, 3H, CH_3).

^{13}C NMR (THF-d_8): δ 174.96; 155.86; 70.96; 61.04; 23.66.

[(4*R*)-4-methyl-2,5-dioxoimidazolidin-4-yl]methanesulfonyl chloride

Following the procedure described for [(4S)-4-methyl-2,5-dioxoimidazolidin-4-yl]methanesulfonyl chloride.

Starting from (5R)-5-methyl-5-{[(phenylmethyl)thio]methyl}imidazolidine-2,4-dione (10.0g, 40mmol).

Obtained 8.78g (96% yield) of the title compound.

Purity by NMR > 98%.

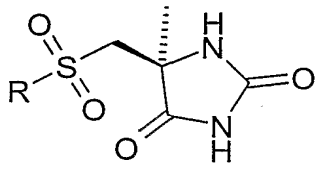
$[\alpha]_D$=+12.8° (c=0.01g/mL, THF, T=20°C).

^{1}H NMR (THF-d_8): δ 9.91 (1H, brs); 7.57 (1H, s); 4.53, 4.44 (1H each, ABq, *J*=14.6Hz); 1.52 (s, 3H, CH_3).

^{13}C NMR (THF-d_8): δ 174.96; 155.84; 70.97; 61.04; 23.66.

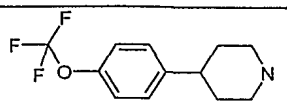
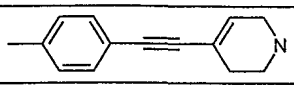
EXAMPLE 18

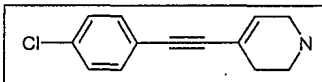
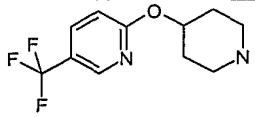
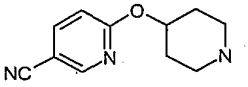
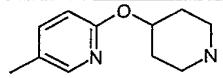
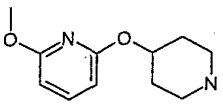
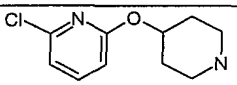
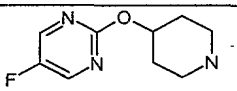
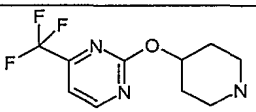
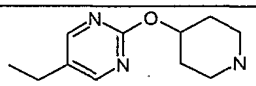
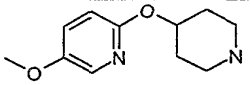
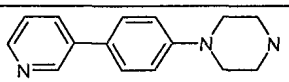
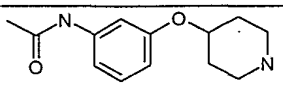
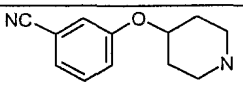
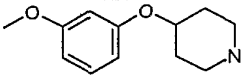
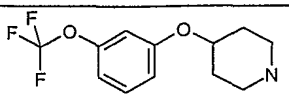
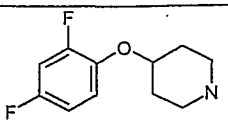
Compounds with the general formula

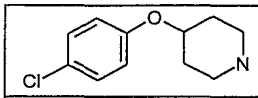
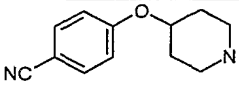
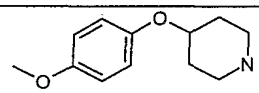
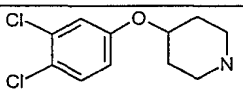
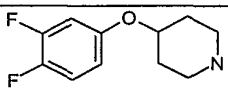
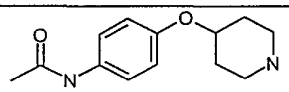
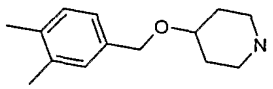
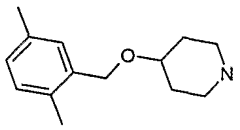
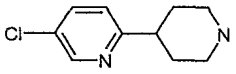
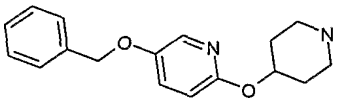
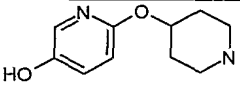
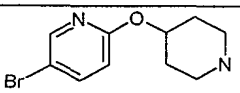
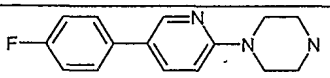
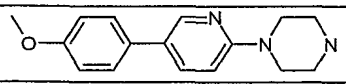
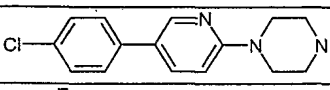
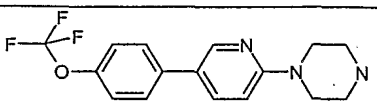
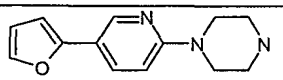


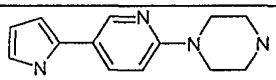
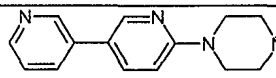
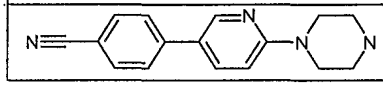
were synthesised according to the method described in Example 17.

AMINE INTERMEDIATES

Amine	Analysis
	m/z 246 (MH+); ^{1}H NMR data
	m/z 185 (MH+); ^{1}H NMR data
	m/z 198 (MH+); ^{1}H NMR data

	m/z 218/220 3:1 (MH+); ^{1}H NMR data
	m/z 247 (MH+); ^{1}H NMR data
	m/z 204 (MH+); ^{1}H NMR data
	^{1}H NMR data
	^{1}H NMR data
	^{1}H NMR data
	^{1}H NMR data
	^{1}H NMR data
	^{1}H NMR data
	m/z 225 (MH+)
	m/z 240 (MH+)
	m/z 235 (MH+)
	m/z 203 (MH+)
	m/z 208(MH+)
	m/z 262 (MH+)
	m/z 214 (MH+)

	m/z 212 (MH+)
	m/z 203 (MH+)
	m/z 208 (MH+)
	m/z 246 (MH+)
	m/z 214 (MH+)
	m/z 235 (MH+)
	m/z 220 (MH+)
	m/z 220 (MH+)
	m/z 197 (MH+); ^{1}H NMR data
	m/z 285 (MH+)
	m/z 195 (MH+); ^{1}H NMR data
	m/z 257, 259 (MH+)
	m/z 258 (MH+)
	m/z 270 (MH+)
	m/z 274, 276 (MH+)
	m/z 324 (MH+)
	m/z 230 (MH+)

	m/z 229 (MH+)
	m/z 241 (MH+)
	m/z 265 (MH+)

All other amines used are commercially available or earlier described.

4-{4-[(trifluoromethyl)oxy]phenyl}piperidine trifluoroacetic acid

$Pd(PPh_3)_4$ (87 mg, 0.0075mmol), LiCl (190 mg, 4.5 mmol), *tert*-butyl 4-{[(trifluoromethyl)sulfonyl]oxy}-3,6-dihydropyridine-1(2*H*)-carboxylate (0.50 g 1.5 mmol), 4-(trifluoromethoxy)phenylboronic acid (0.43 g, 2.1 mmol) and aq Na_2CO_3 (2 mL, 2N solution) were mixed in 5.2 mL DME and heated at 85 °C for 3h followed by cooling to room temperature and concentrated under reduced pressure. The residure was partitioned between DCM (10 mL), aq Na_2CO_3 (10 mL, 2N solution) and conc NH_4OH (0.6 mL). The layers were separated and the aqueous layer extracted with DCM (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification by column chromatography (Si O_2, Heptane/Ethylacetate/DCM 5:1:1) gave *tert*-butyl 4-[4-(trifluoromethoxy)phenyl]-3,6-dihydropyridine-1(2*H*)-carboxylate (0.27g, 52%). The product and 5% Pd/C (30 mg) was mixed in MeOH (3 mL) and stirred under H_2 (1 atm) for 24 h. The mixture was filtered through Celite and concentrated to give *tert*-butyl 4-[4-(trifluoromethoxy)phenyl]piperidine-1-carboxylate (0.23g, 86%). The crude product was dissolved in a mixture of TFA (2 mL) and DCM (4 mL) and stirred at RT for 2 h. The reaction mixture was concentrated and purified by preparative HPLC to give the title compound (0.14 g, 58%, three steps 26%).

LC-MS (APCI) m/z 246 (MH+).

^1H NMR ($CDCl_3$): δ 9.38 (1 H, bs); 8.97 (1 H, bs); 7.26 (2 H, d); 7.20 (2 H, d); 3.60 (2 H, bd); 3.07 (2 H, q); 2.88-2.72 (1 H, m); 2.18-2.01 (4 H, m).

^{19}F NMR ($CDCl_3$): δ –58.35 (3F), –76.19 (3F).

4-[(4-chlorophenyl)ethynyl]-1,2,3,6-tetrahydropyridine hydrochloride

$PdCl_2(PPh_3)_2$ (47 mg, 0.07 mmol) and CuI (13 mg, 0.07 mmol) were dissolved in Et_3N (2.7 mL) and THF (8.4 mL) under a stream of argon and stirred for 10 min. A solution of *tert*-butyl 4-{[(trifluoromethyl)sulfonyl]oxy}-3,6-dihydropyridine-1(2*H*)-carboxylate (0.46 g 1.4 mmol) and 2-ethynylpyridine (152 µL, 1.5 mmol) in 3.5 mL THF was added. The reaction mixture was stirred at RT for 2h, diethyl ether was added and the precipitate was filtered off. The clear solution was washed with saturated aqueous NH_4Cl, water, Brine and dried (Na_2SO_4). Concentration and purification by column chromatography (SiO_2, Heptane/Diethyl ether 1:2*)* gave *tert*-butyl 4-[(4-chlorophenyl)ethynyl]-3,6-dihydropyridine-1(2*H*)-carboxylate (0.26 g, 58%). The product was dissolved in THF (3 mL) and conc HCl (3 mL) and stirred at RT for 30 min. Concentration several times with toluene and EtOH gave the title compound (0.20 g, 98%, two steps 57%).

LC-MS (APCI) m/z 218/220 3:1 (MH+).

^{1}H NMR (DMSO-d_6): δ 9.25 (2 H, bs); 7.49-7.44 (4 H, m); 6.24-6.11 (1 H, m); 3.75-3.63 (2 H, m); 3.25-3.15 (2 H, m); 2.48-2.42 (2 H, m).

The following amines were prepared in a similar way as descibed for 4-[(4-chlorophenyl)ethynyl]-1,2,3,6-tetrahydropyridine hydrochloride.

2-(1,2,3,6-tetrahydropyridine-4-ylethynyl)pyridine

LC-MS (APCI) m/z 185 (MH+).

^{1}H NMR ($CDCl_3$): δ 8.59-8.55 (1 H, m); 7.64 (1 H, dt); 7.43-7.39 (1 H, m); 7.20 (1 H, ddd); 6.30 (1 H, bs); 3.51 (2 H, q); 3.04 (2 H, t); 2.37-2.31 (2 H, m).

4-[(4-methylphenyl)ethynyl]- 1,2,3,6-tetrahydropyridine

LC-MS (APCI) m/z 198 (MH+).

^{1}H NMR ($CDCl_3$): δ 8.91 (1 H, bs); 7.33 (2 H, d); 7.15 (2 H, d); 6.06 (1 H, bs); 3.93-3.80 (2 H, m); 3.49-3.335 (2 H, m); 2.73-2.60 (2 H, m); 2.37 (3 H, s).

2-(Piperidin-4-yloxy)-5-trifluoromethyl-pyridine

Sodium hydride (0.52g, 12 mmol, 55% in oil) was washed twice in hexane, and suspended in dry dimethoxyethane (30 ml). 4-hydroxypiperidine (1.21g, 12 mmol) and 2-chloro-5-trifluoromethylpyridine was dissolved in dry dimethoxyethane (30 ml). The solution was added dropwise to the sodium hydride-suspension. The reaction was stirred at 80 °C under nitrogen over night. After cooling. Water was carefully added to the mixture and the solvents were removed by rotary evaporation. The residue was dissolved in water and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica gel eluting with 80:20:2 EtOAc/MeOH/Et_3N affording 1.7g (63%) of the title compound as a yellow oil, which crystallised after a few hours.

LC-MS (APCI) m/z 247.1 (MH+).

^{1}H NMR ($CDCl_3$): δ 8.40 (1 H, s); 7.74 (1 H, dd, *J*=2.52, 8.70 Hz); 6.78 (1 H, d, *J*=8.74 Hz); 5.25-5.17 (1 H, m); 3.19-3.08 (2 H, m); 2.83-2.73 (2 H, m); 2.10-2.00 (2 H, m); 1.83 (1 H, s); 1.73-1.62 (2 H, m).

The following amines were prepared in a similar way as descibed described in the synthesis of 2-(Piperidin-4-yloxy)-5-trifluoromethyl-pyridine.

6-(Piperidin-4-yloxy)-nicotinonitrile

LC-MS (APCI) m/z 204.2 (MH+).

^{1}H NMR ($CDCl_3$): δ 8.45 (1 H, s); 7.76 (1 H, dd, *J*=2.40, 8.77 Hz); 6.78 (1 H, d, *J*=8.77 Hz); 5.28-5.17 (1 H, m); 3.19-3.09 (2 H, m); 2.83-2.74 (2 H, m); 2.10-2.01 (2 H, m); 1.74-1.63 (2 H, m).

5-Methyl-2-(piperidin-4-yloxy)-pyridine

^{1}H NMR (Methanol-d_4): δ 7.90 (1 H, s); 7.46 (1 H, dd, *J*=2.47, 8.46 Hz); 6.68 (1 H, d, *J*=8.50 Hz); 5.07-4.98 (1 H, m); 3.15-3.07 (2 H, m); 2.82-2.73 (2 H, m); 2.23 (3 H, s); 2.07-1.97 (2 H, m); 1.84-1.74 (2 H, m).

2-Methoxy-6-(piperidin-4-yloxy)-pyridine

^{1}H NMR ($CDCl_3$): δ 7.44 (1 H, t, *J*=7.90 Hz); 7.25 (2 H, dd, *J*=1.83, 7.90 Hz); 5.19-5.11 (1 H, m); 3.82 (3 H, s); 3.23-3.16 (2 H, m); 2.96-2.88 (2 H, m); 2.13-2.05 (2 H, m); 1.89-1.79 (2 H, m).

2-chloro-6-(piperidine-4-yloxy)-pyridine

^{1}H NMR (Methanol-d_4): δ 7.64 (1 H, dd, *J*=7.60, 8.22 Hz); 6.96 (1 H, dd, *J*=0.66, 7.60 Hz); 6.73 (1 H, dd, *J*=0.60, 8.19 Hz); 5.25-5.14 (1 H, m); 3.28-3.18 (2 H, m); 3.05-2.94 (2 H, m); 2.19-2.07 (2 H, m); 1.93-1.80 (2 H, m).

5-Fluoro-2-(piperidin-4-yloxy)-pyrimidine

^{1}H NMR ($CDCl_3$): δ 8.36 (2 H, s); 5.16-5.06 (1 H, m); 3.29-3.18 (2 H, m); 2.98-2.87 (2 H, m); 2.21-2.08 (2 H, m); 1.97-1.81 (2 H, m).

2-(Piperidin-4-yloxy)-4-trifluoromethyl-pyrimidine

^{1}H NMR ($CDCl_3$): δ 8.75 (1 H, d, *J*=4.93 Hz); 7.27 (1 H, d, *J*=5.07 Hz); 5.39-5.30 (1 H, m); 3.44-3.33 (2 H, m); 3.28-3.17 (2 H, m); 2.35-2.10 (4 H, m).

5-Ethyl-2-(piperidin-4-yloxy)-pyrimidine

^{1}H NMR (Methanol-d_4): δ 8.40 (2 H, s); 5.16-5.08 (1 H, m); 3.16-3.06 (2 H, m); 2.77-2.70 (2 H, m); 2.60 (2 H, q, *J*=7.66, 15.28 Hz); 2.10-2.00 (2 H, m); 1.76-1.66 (2 H, m); 1.23 (3 H, t, *J*=7.63 Hz).

5-Methoxy-2-(piperidin-4-yloxy)-pyridine; hydrochloride

4-(5-Methoxy-pyridin-2-yloxy)-piperidine-1-carboxylic acid *tert*-butyl ester (45 mg, 0.14 mmol) was dissolved in THF (3 ml) and conc. HCl (2 ml) was added. The reaction was stirred at room temprature for 2 hrs after which the solvents were removed *in vacuo* and

the remaining water was removed by azeotropic evaporation using EtOH/Toulene affording 35 mg (97%) of the title compound as oily crystals.
LC-MS (APCI) m/z 225.1 (MH+).

The starting material was prepared as follows:

2-Chloro-5-methoxy-pyridine 1-oxide

2-chloro-5-methoxy-pyridine (200 mg, 1.39 mmol) and mCPBA (360 mg, 2.09 mmol) was dissolved in CH_2Cl_2 (10 ml). The mixture was stirred at room temperature for 2 days. The mixture was then diluted with CH_2Cl_2 and washed with 10% aqueous K_2CO_3 and brine and dried over Na_2SO_4. The solvent were removed *in vacuo* affording 140 mg (63%) of the title compound as white crystals.
^{1}H NMR (DMSO-d_6): δ 8.30 (1 H, d, *J*=2.72 Hz); 7.68 (1 H, d, *J*=9.23 Hz); 7.08 (1 H, dd, *J*=2.70, 9.23 Hz); 3.31 (3 H, s).

4-(5-Methoxy-1-oxy-pyridin-2-yloxy)-piperidine-1-carboxylic acid *tert*-butyl ester

Potassium *tert*-butoxide (128 mg, 1.14 mmol) was dissolved in dry THF (10 ml) and 4-Hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester (177 mg, 0.88 mmol) dissolved in dry THF (5 ml) was added under nitrogen. The mixture was stirred at room temperature for 10 minutes after which 2-Chloro-5-methoxy-pyridine 1-oxide (140 mg, 0.88 mmol) dissolved in dry THF (5 ml) was added. The reaction was stirred for 3 days at room temperature. The solvent were removed and the residue was partitioned between H_2O and $CHCl_3$. The organic phase was washed with brine and dried over Na_2SO_4. The solvent were removed *in vacuo* affording 245 mg (86%) of the title compound as a brown oil.
^{1}H NMR ($CDCl_3$): δ 7.95-7.93 (1 H, m); 6.86-6.84 (2 H, m); 4.95-4.85 (1 H, m); 3.79 (3 H, s); 3.25-3.14 (2 H, m); 3.07-2.96 (2 H, m); 1.98-1.79 (4 H, m); 1.46 (9 H, s).

4-(5-Methoxy-pyridin-2-yloxy)-piperidine-1-carboxylic acid *tert*-butyl ester

4-(5-Methoxy-1-oxy-pyridin-2-yloxy)-piperidine-1-carboxylic acid *tert*-butyl ester (200 mg, 0.62 mmol) was dissolved in EtOH (5 ml). Indium (498 mg, 4.34 mmol) and saturated aqueous NH_4Cl (4ml) was added to the solution and the reaction was refluxed for 4 days. The mixture was filtered through celite after cooling and the solvents were removed *in vacuo*. The residue was chromatographed on silica gel eluting with 5:1 Heptane/EtOAc affording 50 mg (26%) of the title compound as a yellowish oil.

^{1}H NMR ($CDCl_3$): δ 7.77 (1 H, d, *J*=3.06 Hz); 7.20 (1 H, dd, *J*=3.07, 8.89 Hz); 6.66 (1 H, d, *J*=8.99 Hz); 5.14-5.07 (1 H, m); 3.80 (3 H, s); 3.79-3.72 (2 H, m); 3.31-3.23 (2 H, m); 2.00-1.91 (2 H, m); 1.75-1.64 (2 H, m); 1.47 (9 H, s).

4-(4-Pyridin-3-yl-phenyl)piperazine; hydrochloride

4-(4-Pyridin-3-yl-phenyl)piperazine-1-carboxylic acid *tert*-butyl ester (60 mg, 0.18 mmol) in THF (3 ml) and conc. HCl (3 ml) was stirred for 1 hr. The solvents were removed in vacuo and the remaining water was removed by azeotropic evaporation using EtOH/Toulene, affording 50 mg (100%) of the title compound as a yellow powder.

LC-MS (APCI) m/z 240.2 (MH+).

The starting material was prepared as follows:

4-(4-Iodophenyl)piperazine-1-carboxylic acid *tert*-butyl ester

was prepared according to La Clair in *Angew. Chem. Int. Ed.*1998, 37(3), 325-329 in 55% overall yield starting from *N*-phenylpiperazine (19 mmol).

4-(4-Pyridin-3-yl-phenyl)piperazine-1-carboxylic acid *tert*-butyl ester

(Ref. Wellmar et al. *J. Heterocycl. Chem.* 32(4), 1995, 1159-1164.)

4-(4-Iodophenyl)piperazine-1-carboxylic acid *tert*-butyl ester (0.272 g, 0.70 mmoles), 3-pyridylboronic acid (0.078 g, 0.64 mmoles), tetrakis(triphenylphosphine)palladium (0.024 g, 0.02 mmoles), 1 M sodium hydrogencarbonate (1.0 mL) and 1,2-dimethoxyethane (1.5

mL) were stirred under nitrogen at 84°C for 3 hours, taken up in ethyl acetate and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate, filtered, concentrated with silica (1 g) by rotary evaporation to give a solid which was applied on a short silica column. Elution with dichloromethane, dichloromethane/ethyl acetate (4:1) and neat ethyl acetate gave 0.060 g (32% yield) of the title compound as a white solid and 0.060 g of starting material (the iodide), respectively. Yield was calculated from amount of converted iodide.

LC-MS (APCI) m/z 340.3 (MH+).

^{1}H NMR (Methanol-d_4): δ 8.75 (1H, d, *J*=2.0 Hz); 8.43 (1H, m); 8.04 (1H, m); 7.58 (2H, d, *J*=8.0 Hz); 7.47 (1H, m); 7.10 (2H, d, *J*=8.0 Hz); 3.59 (4H, m); 3.22 (4H, m); 1.50 (9H, s).

N-[3-(Piperidin-4-yloxy)-phenyl]-acetamide; hydrochloride

4-Hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester (300 mg, 1.5 mmol) was dissolved in dry CH_2Cl_2 and cooled to -10°C. Polymer bound triphenylphosphine (750 mg, 2.25 mmol) was added and allowed to swell. *N*-(3-Hydroxy-phenyl)-acetamide (340 mg, 2.25 mmol) dissolved in dry THF was added and the reaction was stirred at -10°C for 10 minutes after which DEAD (0.35 ml, 2.25 mmol) was added dropwise to the mixture. The reaction was stirred over night allowing the temperature rise to room temperature. The polymer was filtered off, using a short plug of silica with Toluene/EtOAc (5:1) as eluent. The volume of the combined fractions was reduced by rotary evaporation and the solution was washed with 5% aqueous KOH and water, dried over Na_2SO_4 and the solvent removed *in vacuo*. The resulting white powder was dissolved in THF (10 ml) and conc. HCl (10 ml) and stirred at ambient temperature for 1 hr. The solvents were removed *in vacuo* and the remaining water was removed by azeotropic evaporation using EtOH/Toulene, affording 230 mg (57%) of the title compound as a white powder.

LC-MS (APCI) m/z 235.1 (MH+).

The following amines were prepared in a similar way as descibed described in the synthesis N-[3-(Piperidin-4-yloxy)-phenyl]-acetamide.

3-(Piperidin-4-yloxy)-benzonitrile

LC-MS (APCI) m/z 203.2 (MH+).

4-(3-Methoxy-phenoxy)-piperidine

LC-MS (APCI) m/z 208.2 (MH+).

4-(3-Trifluoromethoxy-phenoxy)-piperidine

LC-MS (APCI) m/z 262.1 (MH+).

4-(2,4-Difluoro-phenoxy)-piperidine

LC-MS (APCI) m/z 214.2 (MH+).

4-(4-Chloro-phenoxy)-piperidine

LC-MS (APCI) m/z 212.2 (MH+).

4-(Piperidin-4-yloxy)-benzonitrile

LC-MS (APCI) m/z 203.2 (MH+).

4-(4-Methoxy-phenoxy)-piperidine

LC-MS (APCI) m/z 208.2 (MH+).

4-(3,4-Dichloro-phenoxy)-piperidine

LC-MS (APCI) m/z 246.1 (MH+).

4-(3,4-Difluoro-phenoxy)-piperidine

LC-MS (APCI) m/z 214.2 (MH+).

***N*-[4-(Piperidin-4-yloxy)-phenyl]-acetamide**

LC-MS (APCI) m/z 235.1 (MH+).

4-{[(3,4-dimethylphenyl)methyl]oxy}piperidine hydrochloride

LC-MS (APCI) m/z 220 (MH+).

4-{[(2,5-dimethylphenyl)methyl]oxy}piperidine hydrochloride

LC-MS (APCI) m/z 220 (MH+).

5-chloro-2-piperidin-4-ylpyridine hydrochloride

Zn dust (225 mg, 3.5 mmol) was stirred in THF (1 mL) under Ar and 1,2-dibromoethane (50 μL) was added at room temperature. The mixture was heated to 65 °C for 3 min and allowed to cool to room temperature before trimethylsilyl chloride (70 μL) was added and the mixture was stirred at room temperature for 30 min. A solution of 4-iodo-N-Boc-piperideine (840 mg, 2.7 mmol) in THF (1.5 mL) was slowly added and the reaction mixture was stirred at 40 °C for 2h. $Pd_2(dba)_3$ (22 mg, 0.024 mmol) and $P(2\text{-furyl})_3$ (23 mg, 0.10 mmol) were mixed in THF (0.5 mL), the mixture stirred at room temperature for 10 min and then added to the organozink reagent solution, followed by 2-bromo-5-chloro-pyridine (624 mg, 3.24 mmol) in THF (1 mL) and DMA (4 mL).The reaction mixture was heated at 80 °C for 3 h, allowed to cool to room temperature and then filtered through Celite and diluted with EtOAc. The filtrate was washed with saturated aqueous $NaHCO_3$ and brine, dried Na_2SO_4 and concentrated. Purification on SiO_2 eluting with heptane/EtOAc 95:5 to 2:1 gave *tert*-butyl 4-(5-chloropyridin-2-yl)piperidine-1-carboxylate as an yellow oil (128 mg, 16%). The oil was dissolved in THF (1.5 mL) and conc HCl (1.5 mL) and stirred at RT for 30 min. Concentration several times with toluene and EtOH gave the title compound (89 mg, 89%)

LC-MS (APCI) m/z 197 (MH+).

^{1}H NMR (MeOD-d_4): δ 8.54 (1 H, d); 7.86 (1 H, dd); 7.38 (1 H, d); 3.55-3-45 (2 H, m); 3.22-3.06 (3 H, m); 2.19-2.09 (2 H, m); 2.08-1.98 (2 H, m).

5-Benzyloxy-2-(piperidin-4-yloxy)-pyridine; hydrochloride

The amine was prepared in the same way as described in the synthesis of 5-Methoxy-2-(piperidin-4-yloxy)-pyridine.

LC-MS (APCI) m/z 285 (MH+).

The starting material was prepared as follows:

2-Chloro-5-benzyloxypyridine

Sodium hydride (55% in oil, 236 mg, 5.40 mmol) washed in Hexane and 2-Chloro-5-hydroxypyridine (350 mg, 2.70 mmol) was suspended in dry DMF (20 ml). After 10 minutes at room temperature Benzylbromide (0.32 ml, 2.70 mmol) was added and the mixture was stirred for an additional 2 hrs. The reaction was diluted with water and extracted with EtOAc (3*50 ml). The combined organic layers were washed with water and brine, and dried over Na_2SO_4. The solvent was removed by rotary evaporation, affording 520 mg (88%) of the title compound as a yellow oil.

LC-MS (APCI) m/z 220 (MH+).

^{1}H NMR ($CDCl_3$): δ 8.19 (1H, d, *J*=3.00 Hz); 7.55 (1H, dd, *J*=3.15, 8.81 Hz); 7.48-7.31 (6H, m); 5.19 (2H, s).

2-Chloro-5-benzyloxy-pyridine 1-oxide

The amine was prepared in the same way as described in the synthesis of 2-Chloro-5-methoxy-pyridine 1-oxide.

LC-MS (APCI) m/z 236 (MH+).

^{1}H NMR (DMSO-d_6): δ 8.38 (1H, d, *J*=2.61 Hz); 7.69 (1H, d, *J*=9.28 Hz); 7.47-7.33 (5H, m); 7.15 (1H, dd, *J*=2.69, 9.15 Hz); 5.19 (2H, s).

4-(5-Benzyloxy-1-oxy-pyridin-2-yloxy)-piperidine-1-carboxylic acid *tert*-butyl ester

The compound was prepared as described in the synthesis of 4-(5-Methoxy-1-oxy-pyridin-2-yloxy)-piperidine-1-carboxylic acid *tert*-butyl ester.

LC-MS (APCI) m/z 401 (MH+).

^{1}H NMR (DMSO-d_6): δ 8.12 (1H, d, *J*=2.79 Hz); 7.48-7.32 (5H, m); 7.19 (1H, d, *J*=9.16 Hz); 7.07 (1H, dd, *J*=2.88, 9.18 Hz); 5.13 (2H, s); 4.84-4.76 (1H, m); 3.20-3.11 (2H, m); 3.00-2.87 (2H, m); 1.86-1.78 (2H, m); 1.59-1.49 (2H, m); 1.40 (9H, s).

4-(5-Benzyloxy-pyridin-2-yloxy)-piperidine-1-carboxylic acid *tert*-butyl ester

The compound was prepared as described in the synthesis of 4-(5-Methoxy-pyridin-2-yloxy)-piperidine-1-carboxylic acid *tert*-butyl ester.

LC-MS (APCI) m/z 385 (MH+).

^{1}H NMR ($CDCl_3$): δ 7.86 (1H, d, *J*=3.10 Hz); 7.46-7.32 (5H, m); 7.28 (1H, dd, *J*=3.16, 9.04 Hz); 6.67 (1H, d, *J*=9.04 Hz); 5.16-5.08 (1H, m); 5.05 (2H, s); 3.84-3.72 (2H, m); 3.33-3.25 (2H, m); 2.02-1.93 (2H, m); 1.76-1.66 (2H, m); 1.49 (9H, s).

5-Hydroxy-2-(piperidin-4-yloxy)-pyridine trifluoroacetic acid

4-(5-Benzyloxy-1-oxy-pyridin-2-yloxy)-piperidine-1-carboxylic acid *tert*-butyl ester (476 mg, 1.19 mmol) was dissolved in Methanol (20 ml) and $Pd(OH)_2$ (30 mg) was added. The mixture was hydrogenated at 1 atm and room temperature for 24 hrs. The catalyst was filtered off, and the mixture was purified using preparative HPLC affording, after freeze drying, 110 mg (30%) of the title compound as a TFA-salt and 34 mg (10%) of the neutral Boc-protected intermediate.

LC-MS (APCI) m/z 195 (MH+).

^{1}H NMR (DMSO-d_6): δ 7.66 (1H, d, *J*=2.94 Hz); 7.20 (1H, dd, *J*=3.07, 8.82 Hz); 6.68 (1H, d, *J*=8.93 Hz); 5.12-5.00 (1H, m); 3.29-3.00 (4H, m); 2.16-2.02 (2H, m); 1.93-1.75 (2H, m).

5-Bromo-2-(piperidin-4-yloxy)-pyridine hydrochloride

The amine was prepared in the same way as described in the synthesis of 5-Methoxy-2-(piperidin-4-yloxy)-pyridine.

LC-MS (APCI) m/z 257 + 259 (MH+)

The starting material was prepared as described in the synthesis of 4-(5-Methoxy-pyridin-2-yloxy)-piperidine-1-carboxylic acid *tert*-butyl ester:

4-(5-Bromo-pyridin-2-yloxy)-piperidine-1-carboxylic acid *tert*-butyl ester

LC-MS (APCI) m/z 357 + 359 (MH+).

^{1}H NMR (DMSO-d_6): δ 8.26 (1H, dd, *J*=0.53, 2.67 Hz); 7.88 (1H, dd, *J*=2.66, 8.81 Hz); 6.80 (1H, dd, *J*=0.53, 8.79 Hz); 5.15-5.07 (1H, m); 3.72-3.64 (2H, m); 3.20-3.09 (2H, m); 1.97-1.88 (2H, m); 1.58-1.48 (2H, m); 1.40 (9H, s).

4-(5-(4-Fluoro-phenyl)-pyridine-2-yl)-piperazine hydrochloride

4-(5-(4-Fluoro-phenyl)-pyridine-2-yl)-piperazine-1-carbaldehyde (98 mg, 0.34 mmol) was dissolved in MeOH (5 ml) and conc. HCl (12M, 5 ml) was added. The mixture was stirred at room temperature over night. The solvents were removed *in vacuo* and the remaining water was removed by azeotropic evaporation using EtOH/Toulene affording 102 mg (100%) of the title compound as a yellow powder.

LC-MS (APCI) m/z 258 (MH+).

The starting material was prepared as follows:

4-(5-(4-Fluoro-phenyl)-pyridine-2-yl)-piperazine-1-carbaldehyde

4-(5-Bromo-pyridine-2-yl)-piperazine-1-carbaldehyde (100 mg, 0.37 mmol), 4-Fluorobenzeneboronic acid (55 mg, 0.39 mmol), (1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (10 mg, 0.01 mmol), Toluene (2 ml), EtOH (0.5 ml) and 2M Na_2CO_3 solution (0.5 ml, 1 mmol) were heated at 80°C under N_2 overnight. After cooling the mixture was diluted with toluene and separated. The organic phase was washed with water and brine, filtered through a pad of celite and dried over Na_2SO_4. The solvent were removed *in vacuo* affording 100 mg (94%) of the title product as a beige powder.

LC-MS (APCI) m/z 286 (MH+).

^{1}H NMR (DMSO-d_6): δ 8.44 (1H, d, *J*=2.66 Hz); 8.10 (1H, s); 7.97 (1H, dd, *J*=2.52, 8.82 Hz); 7.70-7.31 (2H, m); 7.31-7.21 (2H, m); 6.97 (1H, d, *J*=8.97 Hz); 3.65-3.43 (8H, m).

The following compounds were synthesised as described in the synthesis of 4-(5-(4-Fluoro-phenyl)-pyridine-2-yl)-piperazine hydrochloride:

4-(5-(4-Methoxy-phenyl)-pyridine-2-yl)-piperazine hydrochloride
LC-MS (APCI) m/z 270 (MH+).

4-(5-(4-Chloro-phenyl)-pyridine-2-yl)-piperazine hydrochloride
LC-MS (APCI) m/z 274, 276 (MH+).

4-(5-(4-Trifluoromethoxy-phenyl)-pyridine-2-yl)-piperazine hydrochloride
LC-MS (APCI) m/z 324 (MH+).

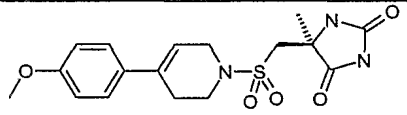
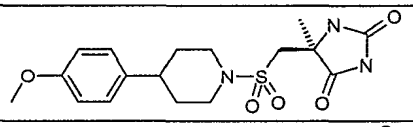
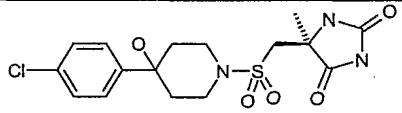
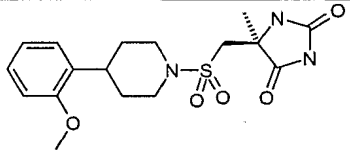
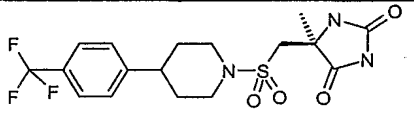
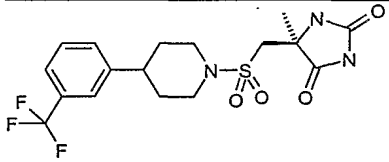
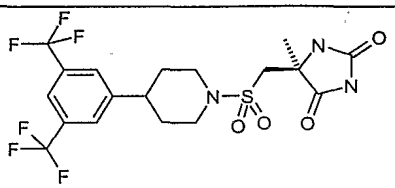
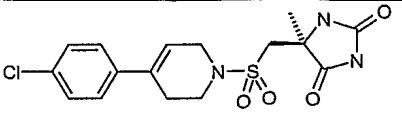
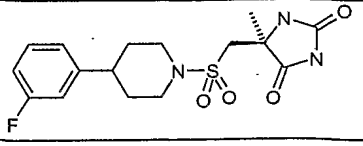
4-(5-Furan-2-yl-pyridine-2-yl)-piperazine hydrochloride
LC-MS (APCI) m/z 230 (MH+).

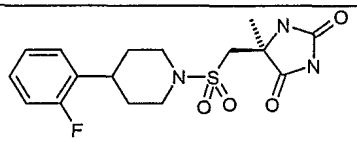
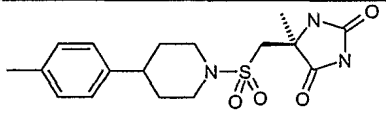
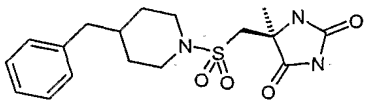
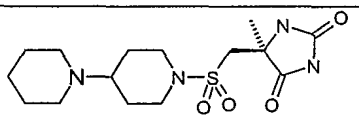
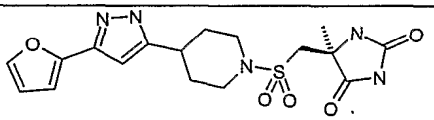
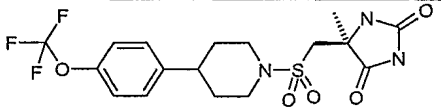
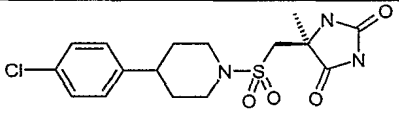
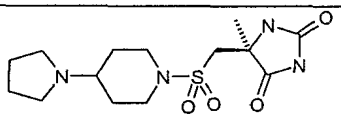
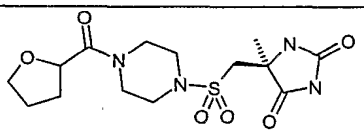
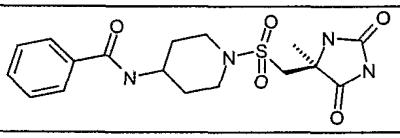
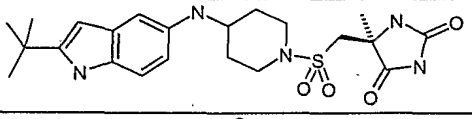
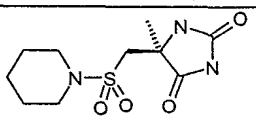
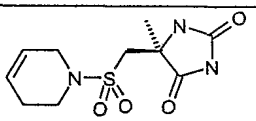
4-(5-(1*H*-Pyrrol-2-yl)-pyridine-2-yl)-piperazine dihydrochloride
The title compound was prepared from 2-(6-(4-Formyl-piperazine-1-yl)-pyridine-3-yl)-pyrrole-1-carboxylic acid *tert*-butyl ester.
LC-MS (APCI) m/z 229 (MH+).

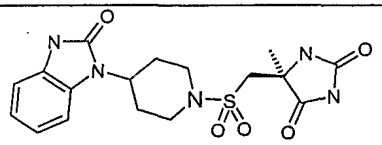
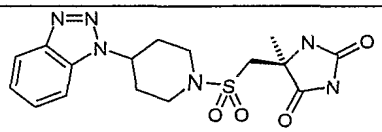
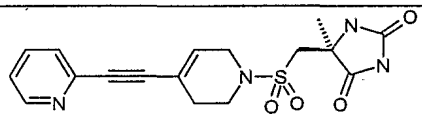
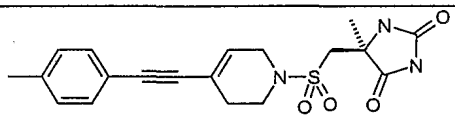
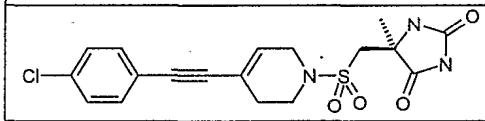
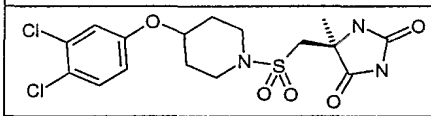
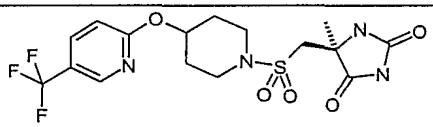
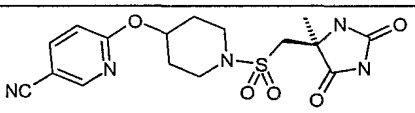
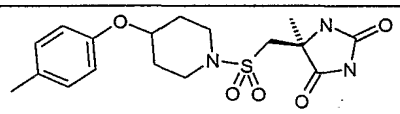
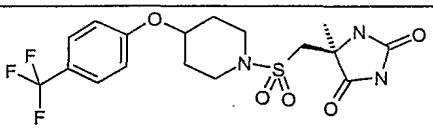
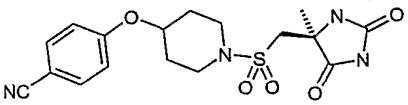
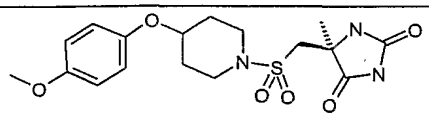
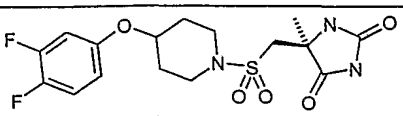
4-[3,3']-Bipyridinyl-6-yl-piperazine hydrochloride
LC-MS (APCI) m/z 241 (MH+).

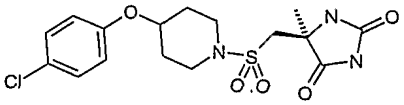
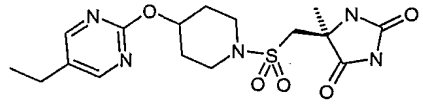
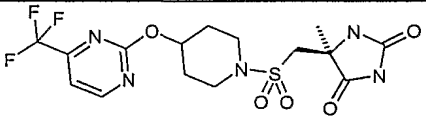
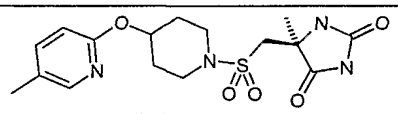
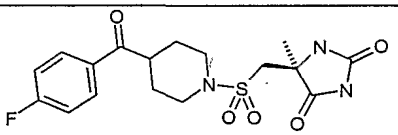
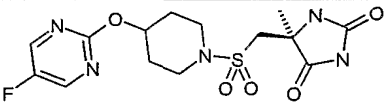
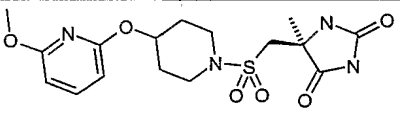
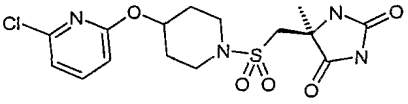
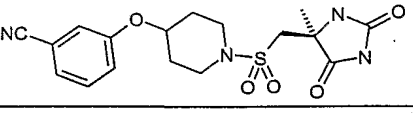
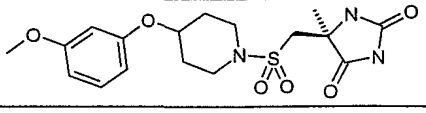
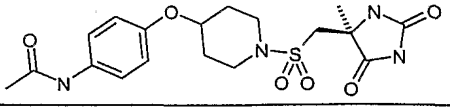
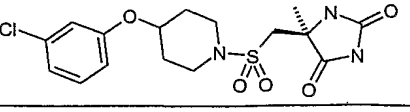
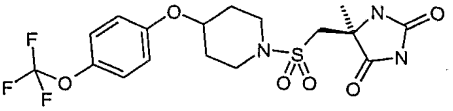
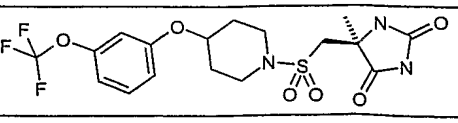
4-(6-Piperazine-1-yl-pyridine-3-yl)-benzonitrile hydrochloride
LC-MS (APCI) m/z 265 (MH+).

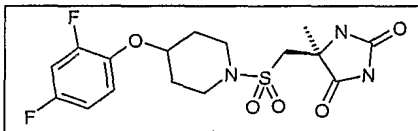
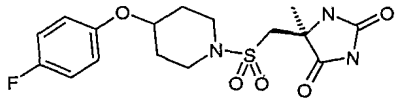
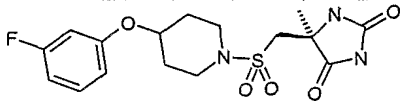
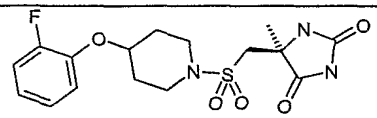
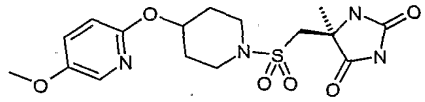
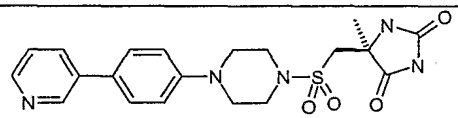
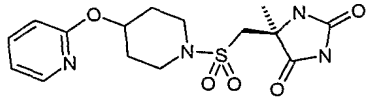
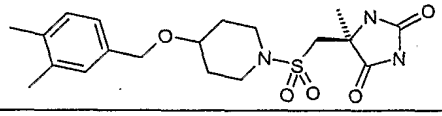
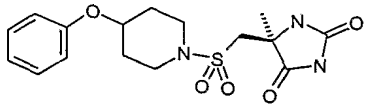
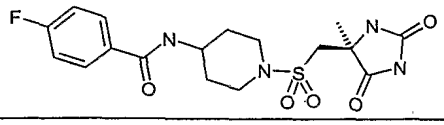
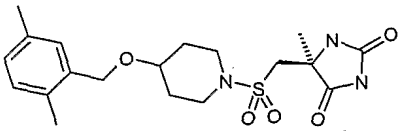
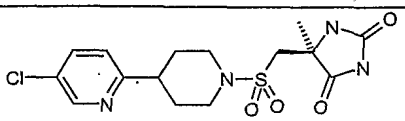
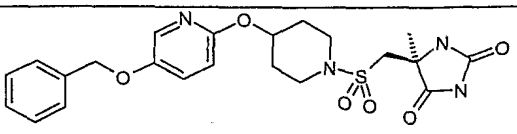
HYDANTOINS OF FORMULA II

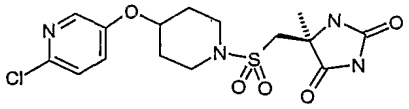
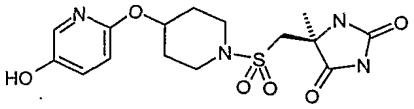
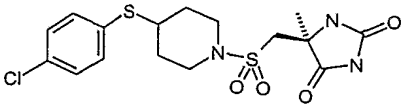
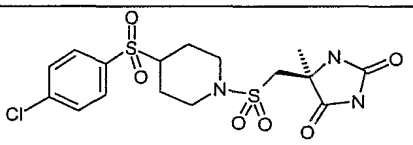
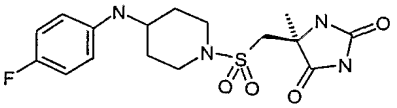
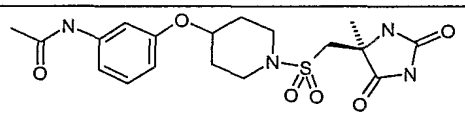
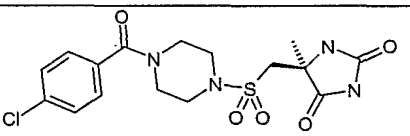
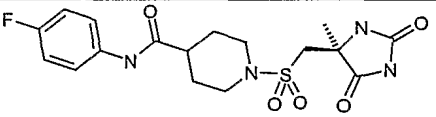
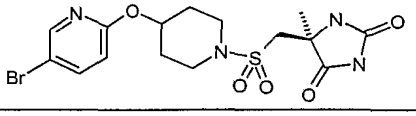
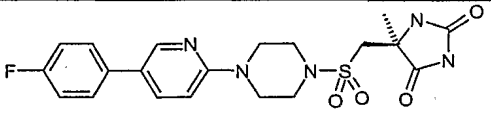
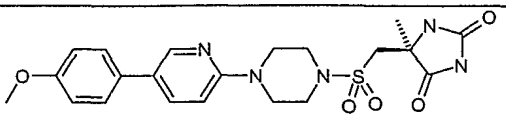
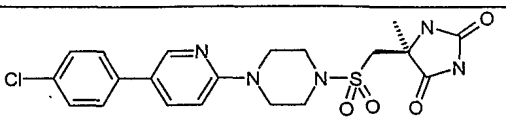
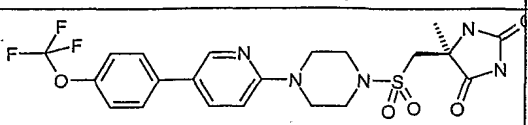
Hydantoin	Analysis[1]
	m/z 380 (MH+)
	m/z 382 (MH+)
	m/z 402/403 3:1 (MH+)
	m/z 382 (MH+)
	m/z 420 (MH+)
	m/z 420 (MH+)
	m/z 488 (MH+)
	m/z 384/386 3:1 (MH+)
	m/z 370 (MH+)

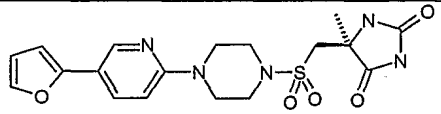
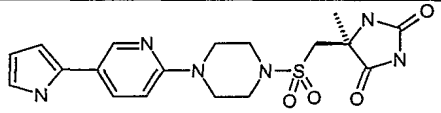
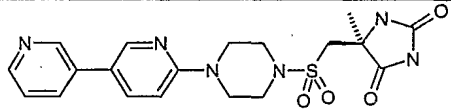
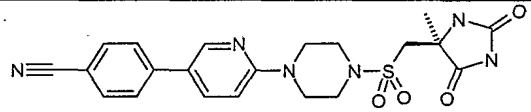
	m/z 370 (MH+)
	m/z 366 (MH+)
	m/z 366 (MH+)
	m/z 359 (MH+)
	m/z 408 (MH+)
	m/z 436 (MH+)
	m/z 386/388 3:1 (MH+)
	m/z 345 (MH+)
	m/z 375 (MH+)
	m/z 395 (MH+)
	m/z 462 (MH+)
	m/z 276 (MH+)
	m/z 274 (MH+)

	m/z 408 (MH+)
	m/z 393 (MH+)
	m/z 375 (MH+)
	m/z 388 (MH+)
	m/z 408 (MH+)
	m/z 436 (MH+)
	m/z 437 (MH+)
	m/z 394 (MH+)
	m/z 382 (MH+)
	m/z 436 (MH+)
	m/z 393 (MH+)
	m/z 398 (MH+)
	m/z 404 (MH+)

	m/z 402 (MH+)
	m/z 398 (MH+)
	m/z 438 (MH+)
	m/z 383 (MH+)
	m/z 398 (MH+)
	m/z 388 (MH+)
	m/z 399 (MH+)
	m/z 403 (MH+)
	m/z 393 (MH+)
	m/z 398 (MH+)
	m/z 425 (MH+)
	m/z 402 (MH+)
	m/z 452 (MH+)
	m/z 452 (MH+)

	m/z 404 (MH+)
	m/z 386 (MH+)
	m/z 386 (MH+)
	m/z 386 (MH+)
	m/z 399 (MH+)
	m/z 430 (MH+)
	m/z 369 (MH+)
	m/z 410 (MH+)
	m/z 368 (MH+)
	m/z 413 (MH+)
	m/z 410 (MH+)
	m/z 387 (MH+)
	m/z 475 (MH+)

	m/z 403 (MH+)
	m/z 385 (MH+)
	m/z 418 (MH+)
	m/z 450 (MH+)
	m/z 385 (MH+)
	m/z 425 (MH+)
	m/z 415 (MH+)
	m/z 413 (MH+)
	m/z 447, 449 (MH+)
	m/z 448 (MH+)
	m/z 460 (MH+)
	m/z 464, 466 (MH+)
	m/z 514 (MH+)

	m/z 420 (MH+)
	m/z 419 (MH+)
	m/z 431 (MH+)
	m/z 455 (MH+)

(1): For NMR-data see experimental part.

The following compounds were prepared in the same way as (5S)-5-({[4-(4-fluorophenyl)piperidin-1-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione (Example 17) and purified either by precipitation and washing with EtOH/water or by preparative HPLC.

(5*S*)-5-methyl-5-({[4-[4-(methyloxy)phenyl]-3,6-dihydropyridin-1(2*H*)-yl]sulfonyl}methyl)imidazolidine-2,4-dione

LC-MS (APCI) m/z 380 (MH+).

^{1}H NMR (Methanol-d_4): δ 7.35 (2 H, d, *J*=8.9 Hz); 6.87 (2 H, d, *J*=8.9 Hz); 6.01 (1 H, dd); 3.92 (2 H, dd); 3.78 (3 H, s); 3.56, 3.41 (1 H each, ABq, *J*=14.6 Hz); 3.51-3.46 (2 H, m); 2.62-2.57 (2 H, m); 1.47 (3 H, s).

(5*S*)-5-methyl-5-[({4-[4-(methyloxy)phenyl]piperidin-1-yl}sulfonyl)methyl]imidazolidine-2,4-dione

LC-MS (APCI) m/z 382 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.73 (1 H, s); 8.01 (1 H, s); 7.17 (2 H, d); 6.85 (2 H, d); 3.71 (3 H, s); 3.60 (2 H, dd); 3.50 (1 H, part of ABq, *J*=14.8 Hz); 2.85 (2 H, q); 2.54 (1 H, t); 1.79 (2 H, d); 1.64-1.53 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-({[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione

LC-MS (APCI) m/z 402/404 3:1 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.72 (1 H, s); 8.01 (1 H, s); 7.51 (2 H, d); 7.37 (2 H, d); 5.22 (1 H, s); 3.49, 3.34 (1 H each, ABq, *J*=14.9 Hz); 3.47-3.35 (2 H, m); 3.15 (2 H, q); 1.93 (2 H, t); 1.64 (2 H, d); 1.33 (3 H, s).

(5*S*)-5-methyl-5-[({4-[2-(methyloxy)phenyl]piperidin-1-yl}sulfonyl)methyl]imidazolidine-2,4-dione

LC-MS (APCI) m/z 382 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.72 (1 H, s); 8.01 (1 H, s); 7.24-7.14 (2 H, m); 6.96 (1 H, d); 6.90 (1 H, t); 3.78 (3 H, s); 3.60 (2 H, dd); 3.51, 3.33 (1 H each, ABq, *J*=14.7 Hz); 3.02-2.94 (1 H, m); 2.88 (2 H, q); 1.77 (2 H, d); 1.66-1.56 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-methyl-5-[({4-[4-(trifluoromethyl)phenyl]piperidin-1-yl}sulfonyl)methyl]imidazolidine-2,4-dione

LC-MS (APCI) m/z 420 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.73 (1 H, s); 8.01 (1 H, s); 7.66 (2 H, d); 7.50 (2 H, d); 3.63 (2 H, dd); 3.52, 3.34 (1 H each, ABq, *J*=14.9 Hz); 2.88 (2 H, ddd); 2.79-2.68 (1 H, m); 1.86 (2 H, d); 1.67 (2 H, ddd); 1.33 (3 H, s).

(5*S*)-5-methyl-5-[({4-[3-(trifluoromethyl)phenyl]piperidin-1-yl}sulfonyl)methyl]imidazolidine-2,4-dione

LC-MS (APCI) m/z 420 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.74 (1 H, s); 8.02 (1 H, s); 7.63-7.52 (4 H, m); 3.63 (2 H, dd); 3.52 (1 H, part of ABq, *J*=14.9 Hz); 2.87 (2 H, ddd); 2.79-2.70 (1 H, m); 1.87 (2 H, d); 1.75-1.63 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-[({4-[3,5-bis(trifluoromethyl)phenyl]piperidin-1-yl}sulfonyl)methyl]-5-methylimidazolidine-2,4-dione

LC-MS (APCI) m/z 488 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.74 (1 H, s); 8.02 (1 H, s); 8.00 (2 H, s); 7.93 (1 H, s); 3.64 (2 H, dd); 3.52 (1 H, part of ABq, *J*=14.9 Hz); 2.95-2.81 (3 H, m); 1.89 (2 H, d); 1.83-1.69 (2 H, m); 1.34 (3 H, s).

(5*S*)-5-({[4-(4-chlorophenyl)-3,6-dihydropyridin-1(2H)-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione

LC-MS (APCI) m/z 384/386 3:1 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.74 (1 H, s); 8.03 (1 H, s); 7.47 (2 H, d); 7.40 (2 H, d); 6.23 (1 H, app s); 3.85 (2 H, app s); 3.52, 3.39 (1 H each, ABq, *J*=14.7 Hz); 3.39-3.32 (2 H, m); 2.55 (2 H, br s); 1.32 (3 H, s).

(5*S*)-5-({[4-(3-fluorophenyl)piperidin-1-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione

LC-MS (APCI) m/z 370 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.73 (1 H, s); 8.01 (1 H, s); 7.38-7.31 (1 H, m); 7.15-7.08 (2 H, m); 7.05-6.98 (1 H, m); 3.62 (2 H, dd); 3.51, 3.33 (1 H each, ABq, *J*=14.7 Hz); 2.95-2.80 (2 H, m); 2.68-2.60 (1 H, m); 1.82 (2 H, br d); 1.69-1.58 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-({[4-(2-fluorophenyl)piperidin-1-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione

LC-MS (APCI) m/z 370 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.73 (1 H, s); 8.01 (1 H, s); 7.36 (1 H, t); 7.30-7.20 (1 H, m); 7.18-7.12 (2 H, m); 3.63 (2 H, dd); 3.52, 3.33 (1 H each, ABq); 2.96-2.85 (3 H, m); 1.80 (2 H, brd); 1.69 (2 H, ddd); 1.33 (3 H, s).

(5*S*)-5-methyl-5-({[4-(4-methylphenyl)piperidin-1-yl]sulfonyl}methyl)imidazolidine-2,4-dione

LC-MS (APCI) m/z 366 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.73 (1 H, s); 8.01 (1 H, s); 7.15-7.07 (4 H, m); 3.60 (2 H, dd); 3.50, 3.32 (1 H each, ABq); 2.85 (2 H, q); 2.59-2.51 (1 H, m); 2.25 (3 H, s); 1.79 (2 H, br d); 1.60 (2 H, ddd).

(5*S*)-5-methyl-5-({[4-(phenylmethyl)piperidin-1-yl]sulfonyl}methyl)imidazolidine-2,4-dione

LC-MS (APCI) m/z 366 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.70 (1 H, s); 7.96 (1 H, s); 7.29-7.15 (5 H, m); 3.46 (2 H, t); 3.41, 3.24 (1 H each, ABq, *J*=14.9 Hz); 2.68 (2 H, dt); 2.52 (2 H, d); 1.54-1.51 (3 H, m); 1.30 (3 H, s).

(5*S*)-5-[(1,4'-bipiperidin-1'-ylsulfonyl)methyl]-5-methylimidazolidine-2,4-dione trifluoroacetic acid

LC-MS (APCI) m/z 359 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.74 (1 H, s); 9.25 (1 H, br s); 8.02 (1 H, s); 3.63 (2 H, t); 3.51, 3.34 (1 H each, ABq, *J*=14.8 Hz); 3.39 (2 H, d); 3.24 (1 H, t); 2.92 (2 H, q); 2.81 (2 H, t); 2.07 (2 H, d); 1.82 (2 H, d); 1.74-1.58 (5 H, m); 1.45-1.34 (1 H, m); 1.31 (3 H, s).

^{19}F NMR (DMSO-d_6): δ –74.48.

(5*S*)-5-({[4-(3-furan-2-yl-1H-pyrazol-5-yl)piperidin-1-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione

LC-MS (APCI) m/z 408 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.73 (1 H, s); 8.01 (1 H, s); 7.66 (1 H, s); 6.64 (1 H, s); 6.53 (1 H, s); 6.34 (1 H, s); 3.61-3.49 (2 H, m); 3.49 (1 H, half ABq, *J*=14.9 Hz); 2.94-2.84 (2 H, m); 2.81-2.72 (1 H, m); 1.98 (2 H, br d); 1.70-1.58 (2 H, m); 1.32 (3 H, s).

(5*S*)-5-methyl-5-{[(4-{4-[(trifluoromethyl)oxy]phenyl}piperidin-1-yl)sulfonyl]methyl}imidazolidine-2,4-dione

LC-MS (APCI) m/z 436 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.73 (1 H, s); 8.01 (1 H, s); 7.40 (2 H, d); 7.28 (2 H, d); 3.70-3.55 (2 H, m); 3.51, 3.33 (1 H each, ABq, *J*=14.7 Hz); 2.94-2.80 (2 H, m); 2.73-2.61 (2 H, m); 1.86 (2 H, d); 1.71-1.57 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-({[4-(4-chlorophenyl)piperidin-1-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione

LC-MS (APCI) m/z 386/388 3:1 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.73 (1 H, s); 8.01 (1 H, s); 7.36-7.28 (4 H, m); 3.66-3.54 (2 H, m); 3.51, 3.33 (1 H each, ABq, *J*=14.9 Hz); 2.92-2.80 (2 H, m); 2.67-2.58 (1 H, m); 1.81 (2 H, br d); 1.68-1.56 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-methyl-5-{[(4-pyrrolidin-1-ylpiperidin-1-yl)sulfonyl]methyl}imidazolidine-2,4-dione trifluoroacetic acid

LC-MS (APCI) m/z 345 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.74 (1 H, s); 9.61 (1 H, br s); 8.01 (1 H, s); 3.60 (2 H, t); 3.51, 3.36 (1 H each, ABq, *J*=14.8 Hz); 3.55-3.47 (2 H, m); 3.27-3.15 (1 H, m); 3.13-3.02 (2 H, m); 2.80 (2 H, t); 2.12 (2 H, br d); 2.07-1.94 (2 H, m); 1.86-1.77 (2 H, m); 1.62-1.49 (2 H, m); 1.32 (3 H, s).

^{19}F NMR (DMSO-d_6): δ −74.02

(5*S*)-5-methyl-5-({[4-(tetrahydrofuran-2-ylcarbonyl)piperazin-1-yl]sulfonyl}methyl)imidazolidine-2,4-dione

LC-MS (APCI) m/z 375 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.73 (1 H, s); 8.01 (1 H, s); 4.65 (1 H, dd); 3.80-3.68 (2 H, m); 3.60-3.42 (3 H and water, m); 3.33 (1 H, half ABq, *J*=14.9 Hz); 3.19-3.00 (4 H, m); 2.09-1.92 (2 H, m); 1.87-1.75 (2 H, m); 1.30 (3 H, s).

N-[1-({[(4*S*)-4-methyl-2,5-dioxoimidazolidin-4-yl]methyl}sulfonyl)piperidin-4-yl]benzamide

LC-MS (APCI) m/z 395 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.72 (1 H, s); 8.30 (1 H, d); 8.01 (1 H, s); 7.82 (2 H, d); 7.51 (1 H, t); 7.45 (2 H, t); 3.96-3.85 (1 H, m); 3.52 (2 H, t); 3.50, 3.32 (1 H each, ABq, *J*=14.7 Hz); 2.92 (2 H, t); 1.88 (2 H, d); 1.55 (2 H, q); 1.33 (3 H, s).

(5*S*)-5-{[(4-{[2-(1,1-dimethylethyl)-1H-indol-5-yl]amino}piperidin-1-yl)sulfonyl]methyl}-5-methylimidazolidine-2,4-dione

LC-MS (APCI) m/z 462 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.72 (1 H, s); 10.37 (1 H, s); 8.00 (1 H, s); 7.02 (1 H, d, *J*=8.4 Hz); 6.58 (1 H, s); 6.45 (1 H, d, *J*=8.4 Hz); 5.86 (1 H, s); 4.65 (1 H, Br s); 3.48, 3.29 (1 H each, ABq, *J*=14.7 Hz); 3.46 (2 H, t); 2.93 (2 H, t); 1.95 (2 H, t); 1.45-1.35 (2 H, m); 1.33 (3 H, s); 1.29 (9 H, s).

(5*S*)-5-methyl-5-[(piperidin-1-ylsulfonyl)methyl]imidazolidine-2,4-dione

LC-MS (APCI) m/z 276 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.70 (1 H, s); 7.97 (1 H, s); 3.44, 3.23 (1 H each, ABq, *J*=14.8 Hz); 3.13-3.01 (4 H, m); 1.58-1.42 (6 H, m); 1.30 (3 H, s).

(5*S*)-5-[(3,6-dihydropyridin-1(2*H*)-ylsulfonyl)methyl]-5-methylimidazolidine-2,4-dione

LC-MS (APCI) m/z 274 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.72 (1 H, s); 8.00 (1 H, s); 5.85-5.78 (1 H, m); 5.74-5.68 (1 H, m); 3.67-3.62 (2 H, m); 3.47, 3.33 (1 H each, ABq, *J*=14.7 Hz); 3.22 (2 H, dd); 2.14-2.10 (2 H, m); 1.31 (3 H, s).

(5*S*)-5-methyl-5-({[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}methyl)imidazolidine-2,4-dione

LC-MS (APCI) m/z 408 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.86 (1 H, s); 10.75 (1 H, s); 8.02 (1 H, s); 7.27-7.17 (1 H, m); 7.05-6.91 (3 H, m); 4.38-4.20 (1 H, m); 3.65 (2 H, t); 3.56, 3.38 (1 H each, ABq, *J*=14.8 Hz); 3.03-2.90 (2 H, m); 2.41-2.24 (2 H, m); 1.76 (2 H, d); 1.34 (3 H, s).

(5*S*)-5-({[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione

LC-MS (APCI) m/z 393 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.77 (1 H, s); 8.05 (1 H, s); 8.05 (1 H, d); 7.93 (1 H, d); 7.56 (1 H, t); 7.41 (1 H, t); 5.12-4.97 (1 H, m); 3.71 (2 H, t); 3.58, 3.43 (1 H each, ABq, *J*=14.7 Hz); 3.19-3.03 (2 H, m); 2.29-2.16 (4 H, m); 1.35 (3 H, s).

(5*S*)-5-methyl-5-({[4-(pyridin-2-ylethynyl)-3,6-dihydropyridin-1(2*H*)-yl]sulfonyl}methyl)imidazolidine-2,4-dione trifluoroacetic acid

LC-MS (APCI) m/z 375 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.57 (1 H, s); 8.56 (1 H, d); 8.03 (1 H, s); 7.82 (1 H, t); 7.53 (1 H, d); 7.38 (1 H, dd); 6.31 (1 H, br s); 3.83 (2 H, d); 3.54, 3.41 (1 H each, ABq, *J*=14.8 Hz); 3.36-3.25 (2 H, m); 2.42-2.34 (2 H, m); 1.32 (3 H, s).

^{19}F NMR (DMSO-d_6): δ –75.10

(5*S*)-5-methyl-5-({[4-[(4-methylphenyl)ethynyl]-3,6-dihydropyridin-1(2*H*)-yl]sulfonyl}methyl)imidazolidine-2,4-dione

LC-MS (APCI) m/z 388 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.74 (1 H, s); 8.02 (1 H, s); 7.32 (2 H, d); 7.19 (2 H, d); 6.17 (1 H, br s); 3.80 (2 H, d); 3.52, 3.39 (1 H each, ABq, *J*=14.8 Hz); 3.29 (2 H, t); 2.39-2.32 (2 H, m); 2.30 (3 H, s); 1.32 (3 H, s).

(5*S*)-5-({[4-[(4-chlorophenyl)ethynyl]-3,6-dihydropyridin-1(2*H*)-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione

LC-MS (APCI) m/z 408 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.74 (1 H, s); 8.02 (1 H, s); 7.54-7.38 (4 H, m); 6.23 (1 H, br s); 3.87-3.76 (2 H, m); 3.53, 3.41 (1 H each, ABq, *J*=14.9 Hz); 3.34-2.25 (2 H, m); 2.42-2.29 (2 H, m); 1.32 (3 H, s).

(5*S*)-5-[4-(3,4-Dichloro-phenoxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z (APCI) m/z 436.1 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.74 (1 H, s); 8.01 (1 H, s); 7.53 (1 H, d, *J*=9.2 Hz); 7.31 (1 H, d, *J*=2.9 Hz); 7.02 (1 H, dd, *J*=9.2, 2.9 Hz); 4.65-4.57 (1 H, m); 3.51, 3.34 (1 H each, ABq, *J*=15.2 Hz); 3.39-3.27 (2 H, m); 3.17-3.08 (2 H, m); 2.00-1.90 (2 H, m); 1.75-1.65 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-[4-(5-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 403.3 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.74 (1 H, s); 8.20 (1 H, d, *J*=2.7 Hz); 7.81 (1 H, dd, *J*=8.7, 2.7 Hz); 6.87 (1 H, d, *J*=2.7 Hz); 5.16-5.03 (1 H, m); 3.52, 3.35 (1 H each, ABq, *J*=15.0 Hz); 3.43-3.28 (2 H, m); 3.19-3.07 (2 H, m); 2.08-1.95 (2 H, m); 1.80-1.65 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-Methyl-5-[4-(5-trifluoromethyl-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-imidazolidine-2,4-dione

LC-MS (APCI) m/z 437 (MH+).

^{1}H NMR ($CDCl_3$): δ 8.95 (1 H, s); 8.42-8.38 (1 H, m); 7.79 (1 H, dd, *J*=8.8, 2.5 Hz); 6.81 (1 H, d, *J*=8.8 Hz); 6.71 (1 H, s); 5.40-5.28 (1 H, m); 3.52-3.39 (2 H, m); 3.40-3.28 (2 H, m); 3.32 (2 H, ABq, *J*=24.6, 14.0 Hz); 2.16-2.02 (2 H, m); 2.02-1.84 (2 H, m); 1.67 (3 H, s).

6-[1-((4*S*)-4-Methyl-2,5-dioxo-imidazolidin-4-ylmethanesulfonyl)-piperidin-4-yloxy]-nicotinonitrile

LC-MS (APCI) m/z 394.3 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.72 (1 H, s); 8.68 (1 H, d, *J*=2.3 Hz); 8.14 (1 H, dd, *J*=8.7, 2.3 Hz); 8.00 (1 H, s); 6.98 (1 H, d, *J*=8.7 Hz); 5.27-5.14 (1 H, m); 3.56-3.28 (4 H, m); 3.18-3.06 (2 H, m); 2.08-1.96 (2 H, m); 1.81-1.66 (2 H, m); 1.31 (3 H, s).

(5*S*)-5-Methyl-5-(4-*p*-tolyloxy-piperidine-1-sulfonylmethyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 382.5 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.73 (1 H, s); 8.01 (1 H, s); 7.09 (2 H, d, *J*=8.4 Hz); 6.87 (2 H, d, *J*=8.4 Hz); 4.50-4.42 (1 H, m); 3.50, 3.34 (1 H each, ABq, *J*=14.8 Hz); 3.38-3.29 (2 H, m); 3.17-3.09 (2 H, m); 2.23 (3 H, s); 1.99-1.89 (2 H, m); 1.73-1.63 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-Methyl-5-[4-(4-trifluoromethyl-phenoxy)-piperidine-1-sulfonylmethyl]-imidazolidine-2,4-dione

LC-MS (APCI) m/z 436.3 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.71 (1 H, brs); 8.02 (1 H, s); 7.65 (2 H, d, *J*=8.8 Hz); 7.17 (2 H, d, *J*=8.8 Hz); 4.72-4.64 (1 H, m); 3.52, 3.35 (1 H each, ABq, *J*=14.7 Hz); 3.40-3.28 (2 H, m); 3.19-3.10 (2 H, m); 2.05-1.95 (2 H, m); 1.78-1.68 (2 H, m); 1.33 (3 H, s).

4-[1-(4*S*)-4-Methyl-2,5-dioxo-imidazolidin-4-ylmethanesulfonyl)-piperidin-4-yloxy]-benzonitrile

LC-MS (APCI) M/Z 393.2 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.73 (1 H, s); 8.00 (1 H, s); 7.76 (2 H, d, *J*=8.8 Hz); 7.15 (2 H, d, *J*=8.8 Hz); 4.74-4.65 (1 H, m); 3.51, 3.34 (1 H each, ABq, *J*=14.9 Hz); 3.40-3.27 (2 H, m); 3.17-3.07 (2 H, m); 2.03-1.94 (2 H, m); 1.77-1.66 (2 H, m); 1.32 (3 H, s).

(5*S*)-5-[4-(4-Methoxy-phenoxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 398.2 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.73 (1 H, s); 8.01 (1 H, s); 6.89 (4 H, ABq, *J*=29.1, 9.1 Hz); 4.43-4.34 (1 H, m); 3.70 (3 H, m); 3.51, 3.33 (1 H, ABq, *J*=15.0 Hz); 3.38-3.28 (2 H, m); 3.16-3.05 (2 H, m); 1.97-1.87 (2 H, m); 1.73-1.62 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-[4-(3,4-Difluoro-phenoxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 404.2 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.74 (1 H, s); 8.01 (1 H, s); 7.35 (1 H, q, *J*=19.6, 9.2 Hz); 7.19-7.11 (1 H, m); 6.86-6.80 (1 H, m); 4.57-4.48 (1 H, m); 3.51, 3.34 (1 H each, ABq, *J*=14.9 Hz); 3.38-3.28 (2 H, m); 2.16-2.06 (2 H, m); 2.00-1.90 (2 H, m); 1.74-1.64 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-[4-(4-Chloro-phenoxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 402 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.73 (1 H, s); 8.00 (1 H, s); 7.32 (2 H, d, *J*=8.8 Hz); 7.00 (2 H, d, *J*=8.8 Hz); 4.56-4.48 (1 H, m); 3.50, 3.33 (1 H each, ABq, *J*=14.8 Hz); 3.37-3.28 (2 H, m); 3.16-3.06 (2 H, m); 2.00-1.90 (2 H, m); 1.73-1.63 (2 H, m); 1.32 (3 H, s).

(5*S*)-5-[4-(5-Ethyl-pyrimidin-2-yloxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 398 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.74 (1 H, s); 8.47 (2 H, s); 8.02 (1 H, s); 5.11-5.03 (1 H, m); 3.52, 3.35 (1 H each, ABq, *J*=14.8 Hz); 3.42-3.28 (2 H, m); 3.19-3.10 (2 H, m); 2.54 (2 H, q, *J*=15.2, 7.6 Hz); 2.06-1.98 (2 H, m); 1.81-1.71 (2 H, m); 1.33 (3 H, s); 1.17 (3 H, t, *J*=7.2 Hz).

(5*S*)-5-Methyl-5-[4-(4-trifluoromethyl-pyrimidin-2-yloxy)-piperidine-1-sulfonylmethyl]-imidazolidine-2,4-dione

LC-MS (APCI) m/z 438 (MH+).

^{1}H NMR ($CDCl_3$): δ 8.84-8.76 (1 H, m); 8.02 (1 H, s); 7.31 (1 H, d, *J*=4.8 Hz); 6.33 (1 H, s); 5.41-5.34 (1 H, m); 4.54-4.42 (4 H, m); 3.35, 3.24 (1 H each, ABq, *J*=12.9 Hz); 2.17-2.07 (4 H, m); 2.02 (3 H, s).

(5*S*)-5-Methyl-5-[4-(5-methyl-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-imidazolidine-2,4-dione

LC-MS (APCI) m/z 383 (MH+).

^{1}H NMR ($CDCl_3$): δ 8.14 (1 H, s); 8.06-7.99 (2 H, m); 7.19 (1 H, s); 7.09 (1 H, d, *J*=11.6 Hz); 5.28-5.21 (1 H, m); 3.70-3.41 (6 H, m); 2.44 (3 H, s); 2.13-1.96 (4 H, m); 1.62 (3 H, s).

(5*S*)-5-[4-(4-Fluoro-benzoyl)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 398 (MH+).

^{1}H NMR (DMSO- d_6): δ 8.06 (2 H, q, *J*=9.2, 6.0 Hz); 7.40 (2 H, t, *J*=8.8 Hz); 3.61-3.41 (4 H, m); 3.00-2.91 (2 H, m); 1.90-1.81 (2 H, m); 1.62-1.50 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-[4-(5-Fluoro-pyrimidin-2-yloxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 388 (MH+).

^{1}H NMR ($CDCl_3$): δ 8.42 (2 H, s); 8.30 (1 H, s); 6.40 (1 H, s); 5.30-5.23 (1 H, m); 3.53-3.35 (4 H, m); 3.36, 3.21 (1 H each, ABq, *J*=14.4 Hz); 2.10-2.02 (4 H, m); 1.70 (3 H, s).

(5*S*)-5-[4-(6-Methoxy-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 399 (MH+).

^{1}H NMR (MeOD): δ 7.54 (1 H, t, *J*=8.4 Hz); 6.33-6.28 (2 H, m); 5.24-5.14 (1 H, m); 3.86 (3 H, s); 3.53-3.42 (2 H, m); 3.58, 3.39 (1 H each, ABq, *J*=14.4 Hz); 3.30-3.22 (2 H, m); 2.13-2.02 (2 H, m); 1.96-1.82 (2 H, m); 1.47 (3 H, s).

(5*S*)-5-[4-(6-Chloro-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 403 (MH+).

^{1}H NMR (MeOD): δ 7.65 (1 H, t, *J*=7.8 Hz); 6.97 (1 H, d, *J*=7.2 Hz); 6.73 (1 H, d, *J*=7.2 Hz); 5.25-5.14 (1 H, m); 3.55-3.44 (2 H, m); 3.58, 3.39 (1 H each, ABq, *J*=14.4 Hz); 3.28-3.19 (2 H, m); 2.14-2.02 (2 H, m); 1.92-1.79 (2 H, m); 1.47 (3 H, s).

3-[1-((4*S*)-4-Methyl-2,5-dioxo-imidazolidin-4-ylmethanesulfonyl)-piperidin-4-yloxy]-benzonitrile

LC-MS (APCI) m/z 393 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.74 (1 H, s); 8.02 (1 H, s); 7.52-7.47 (2 H, m); 7.42-7.38 (1 H, m); 7.36-7.31 (1 H, m); 4.69-4.61 (1 H, m); 3.52, 3.35 (1 H each, ABq, *J*=17.2 Hz); 3.18-3.07 (2 H, m); 2.02-1.95 (2 H, m); 1.79-1.65 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-[4-(3-Methoxy-phenoxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 398 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.74 (1 H, s); 8.01 (1 H, s); 7.21-7.15 (1 H, m); 6.58-6.50 (3 H, m); 4.57-4.49 (1 H, m); 3.73 (3 H, s); 3.51, 3.34 (1 H each, ABq, *J*=14.4 Hz); 3.17-3.08 (2 H, m); 2.01-1.91 (2 H, m); 1.74-1.64 (2 H, m); 1.33 (3 H, s).

***N*-{4-[1-((4*S*)-4-Methyl-2,5-dioxo-imidazolidin-4-ylmethanesulfonyl)-piperidin-4-yloxy]-phenyl}-acetamide**

LC-MS (APCI) m/z 425 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.69 (1 H, brs); 9.78 (1 H, s); 8.00 (1 H, s); 7.47 (2 H, d, *J*=9.2 Hz); 6.91 (2 H, d, *J*=9.2 Hz); 4.48-4.41 (1 H, m); 3.51 (1 H from ABq, *J*=14.4 Hz); 3.16-3.06 (2 H, m); 2.00 (3 H, s); 1.98-1.90 (2 H, m); 1.73-1.63 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-[4-(3-Chloro-phenoxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 402 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.76 (1 H, brs); 7.99 (1 H, s); 7.31 (1 H, t, *J*=8.4 Hz); 7.08 (1 H, t, *J*=2.2 Hz); 7.02-6.95 (2 H, m); 4.64-4.56 (1 H, m); 3.51 (1 H from ABq, *J*=14.4 Hz); 3.17-3.09 (2 H, m); 2.00-1.91 (2 H, m); 1.75-1.65 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-Methyl-5-[4-(4-trifluoromethoxy-phenoxy)-piperidine-1-sulfonylmethyl]-imidazolidine-2,4-dione

LC-MS (APCI) m/z 452 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.74 (1 H, s); 8.01 (1 H, s); 7.29 (2 H, d, *J*=8.8 Hz); 7.08 (2 H, d, *J*=9.2 Hz); 4.60-4.52 (1 H, m); 3.51 (1 H from ABq, *J*=14.8 Hz); 3.17-3.08 (2 H, m); 2.02-1.93 (2 H, m); 1.75-1.65 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-Methyl-5-[4-(3-trifluoromethoxy-phenoxy)-piperidine-1-sulfonylmethyl]-imidazolidine-2,4-dione

LC-MS (APCI) m/z 452 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.74 (1 H, s); 8.01 (1 H, s); 7.41 (1 H, t, *J*=8.4 Hz); 7.06-6.91 (3 H, m); 4.65-4.58 (1 H, m); 3.51 (1 H from ABq, *J*=14.8 Hz); 3.18-3.08 (2 H, m); 2.02-1.93 (2 H, m); 1.76-1.65 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-[4-(2,4-Difluoro-phenoxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 404 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.74 (1 H, s); 8.02 (1 H, s); 7.34-7.23 (2 H, m); 7.06-6.97 (1 H, m); 4.50-4.41 (1 H, m); 3.50 (1 H from ABq); 3.17-3.06 (2 H, m); 2.02-1.90 (2 H, m); 1.78-1.65 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-[4-(4-Fluoro-phenoxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 386 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.75 (1 H, s); 8.02 (1 H, s); 7.17-6.97 (2 H, m); 4.52-4.43 (1 H, m); 3.17-3.06 (2 H, m); 2.00-1.89 (2 H, m); 1.75-1.62 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-[4-(3-Fluoro-phenoxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 386 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.72 (1 H, s); 8.02 (1 H, s); 7.36-7.26 (1 H, m); 6.91-6.71 (3 H, m); 4.62-4.52 (1 H, m); 3.18-3.06 (2 H, m); 2.02-1.91 (2 H, m); 1.78-1.63 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-[4-(2-Fluoro-phenoxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 386 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.74 (1 H, s); 8.01 (1 H, s); 7.28-7.17 (2 H, m); 7.17-7.08 (1 H, m); 7.02-6.97 (1 H, m); 4.59-4.47 (1 H, m); 2.04-1.92 (2 H, m); 1.80-1.67 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-[4-(5-Methoxy-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 399 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.74 (1 H, s); 8.01 (1 H, s); 7.89 (1 H, d, *J*=3.16 Hz); 7.39 (1 H, dd, *J*=3.18, 9.07 Hz); 6.77 (1 H, d, *J*=8.95 Hz); 5.08-4.96 (1 H, m); 3.76 (3 H, s); 3.51, 3.34 (1 H each, ABq, *J*=14.7 Hz); 3.43-3.29 (2 H, m); 3.18-3.05 (2 H, m); 2.05-1.94 (2 H, m); 1.77-1.61 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-Methyl-5-[4-(4-pyridin-3-yl-phenyl)-piperazine-1-sulfonylmethyl]-imidazolidine-2,4-dione

LC-MS (APCI) m/z 430 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.76 (1 H, s); 8.99 (1 H, s); 8.60 (1 H, d, *J*=4.91 Hz); 8.35 (1 H, d, *J*=7.81 Hz); 8.04 (1 H, s); 7.70 (2 H, d, *J*=8.87 Hz); 7.12 (2 H, d, *J*=8.91 Hz); 3.57 (1 H from ABq); 3.35 (4 H, m); 3.27 (4 H, m); 1.33 (3 H, s).

(5*S*)-5-methyl-5-({[4-(pyridin-2-yloxy)piperidin-1-yl]sulfonyl}methyl)imidazolidine-2,4-dione

LC-MS (APCI) m/z 369 (MH+).

^{1}H NMR ($CDCl_3$): δ 1.73 (3H, s); 1.96-2.04 (2H, m); 2.04-2.13 (2H, m); 3.21 (1H, d); 3.36-3.42 (3H, m); 3.45-3.50 (2H, m); 5.29-5.33 (1H, m); 6.30 (1H, bs); 6.78 (1H, d); 6.93 (1H, t); 7.65 (1H, t); 7.70 (1H, bs); 8.16 (1H, d).

(5*S*)-5-[({4-[(3,4-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)methyl]-5-methylimidazolidine-2,4-dione

(NB. contains 30% of the 2,3-dimethyl isomer which was in the starting material)

LC-MS (APCI) m/z 410 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.3 (3H, s); 1.53-1.64 (2H, m); 1.83-1.89 (2H, m); 2.18 (3H, s); 2.20 (3H, s); 2.95-3.33 (2H, m); 3.25-3.31 (3H, m); 3.45 (1H, d); 3.45-3.53 (1H, m); 4.42 (2H, s); 7.01-7.15 (3H, m); 7.97 (1H, s); 10.70 (1H, s).

(5*S*)-5-methyl-5-{[(4-phenoxypiperidin-1-yl)sulfonyl]methyl}imidazolidine-2,4-dione

LC-MS (APCI) m/z 368 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.30 (3H, s); 1.64-1.73 (2H, m); 1.92-2.00 (2H, m); 3.08-3.15 (2H, m); 3.28-3.44 (4H, m); 4.49-4.54 (1H, m); 6.92 (1H, t); 6.96 (2H, d); 7.28 (2H, t); 7.69 (1H, bs); 10.7 (1H, bs).

4-Fluoro-*N*-[1-((4*S*)-4-methyl-2,5-dioxo-imidazolidin-4-ylmethanesulfonyl)-piperidin-4-yl]-benzamide

LC-MS (APCI) m/z 413 (MH+).

^{1}H NMR (DMSO- d_6): δ 10.73 (1 H, s); 8.34 (1 H, d, *J*=7.50 Hz); 8.02 (1 H, s); 7.94-7.88 (2 H, m); 7.33-7.26 (2 H, m); 3.96-3.86 (1 H, m); 3.58-3.47 (2 H, m); 3.51, 3.32 (1 H each, ABq, *J*=14.81 Hz); 2.97-2.88 (2 H, m); 1.92-1.84 (2 H, m); 1.62-1.48 (2 H, m); 1.33 (3 H, s).

(5*S*)-5-[({4-[(2,5-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)methyl]-5-methylimidazolidine-2,4-dione

LC-MS (APCI) m/z 410 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.30 (3H, s); 1.54-1.62 (2H, m); 1.85-1.91 (2H, m); 2.21 (3H, s); 2.24 (3H, s); 2.97-3.03 (2H, m); 3.27-3.34 (3H, m); 3.45 (1H, d); 3.49-3.55 (1H, m); 6.97-7.04 (2H, m); 7.11 (1H, s); 7.98 (1H, s); 10.70 (1H, s).

(5*S*)- 5-{[4-(5-chloropyridin-2-yl)piperidin-1-yl]sulfonyl}-5-methylimidazolidine-2,4-dione

LC-MS (APCI) m/z 387 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.72 (1 H, s); 8.54 (1 H, d); 8.01 (1 H, s); 7.86 (1 H, dd); 7.38 (1 H, d); 3.61 (2 H, bt); 3.50, 3.32 (1 H each, ABq, *J*=14.9 Hz); 2.96-2.76 (3 H, m); 1.92 (2 H, brd); 1.77-1.62 (2 H, m); 1.33 (3 H, s).

(5S)-5-[4-(5-Benzyloxy-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 475 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.73 (1H, s); 8.01 (1H, s); 7.90 (1H, d, *J*=3.13 Hz); 7.48-7.30 (6H, m); 6.76 (1H, d, *J*=8.97 Hz); 5.10 (2H, s); 5.05-4.98 (1H, m); 3.51 (1H (from ABq), *J*=14.84 Hz); 3.40-3.30 (3H, m); 3.15-3.07 (2H, m); 2.07-1.95 (2H, m); 1.74-1.64 (2H, m); 1.33 (3H, s).

(5S)-5-[4-(6-Chloro-pyridine-3-yloxy)-piperidine-1-sulfonylmethyl] -5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 403 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.74 (1H, s); 8.17 (1H, d, *J*=3.10 Hz); 8.01 (1H, s); 7.56 (1H, dd, *J*=3.18, 8.80 Hz); 7.44 (1H, d, *J*=8.77 Hz); 4.67-4.59 (1H, m); 3.52, 3.35 (2H, ABq, *J*=15.22 Hz); 3.39-3.28 (2H, m); 3.17-3.08 (2H, m); 2.03-1.93 (2H, m); 1.77-1.67 (2H, m); 1.33 (3H, s).

(5S)-5-[4-(5-Hydroxy-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 385 (MH+).

^{1}H NMR (Methanol-d_4): δ 7.73 (1H, d, *J*=3.01 Hz); 7.53 (1H, dd, *J*=3.11, 9.03 Hz); 7.04

(1H, d, *J*=9.04 Hz); 3.80-3.67 (1H, m); 3.58, 3.41 (2H, ABq, *J*=15.04 Hz); 3.53-3.42 (2H, m); 3.36-3.18 (2H, m); 2.17-2.02 (2H, m); 1.96-1.81 (2H, m); 1.48 (3H, s).

(5S)-5-[4-(4-Chloro-phenylsulfanyl)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 418 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.74 (1H, s); 8.00 (1H, s); 7.45-7.39 (4H, m); 2.97-2.89 (2H, m); 2.00-1.91 (2H, m); 1.56-1.45 (2H, m); 1.31 (3H, s).

(5S)-5-[4-(4-Chloro-benzenesulfonyl)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 450 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.73 (1H, s); 7.99 (1H, s); 7.86 (2H, d, *J*=8.77 Hz); 7.77 (2H, d, *J*=8.75 Hz); 3.66-3.54 (2H, m); 3.50-3.41 (1H, m); 3.44, 3.32 (1H each, ABq, *J*=14.63 Hz); 2.82-2.73 (2H, m); 1.97-1.88 (2H, m); 1.57-1.42 (2H, m); 1.30 (3H, s).

(5S)-5-[4-(4-Fluoro-phenylamino)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 385 (MH+).

^{1}H NMR (Methanol-d_4): δ 7.20-7.11 (4H, m); 3.84-3.71 (2H, m); 3.60-3.48 (1H, m); 3.56, 3.39 (1H each, ABq, *J*=14.96 Hz); 2.97-2.84 (2H, m); 2.10-2.00 (2H, m); 1.69-1.53 (2H, m); 1.46 (3H, s).

N-{3-[1-((4S)-4-Methyl-2,5-dioxo-imidazolidin-4-ylmethanesulfonyl)-piperidin-4-yloxy]-phenyl}-acetamide

LC-MS (APCI) m/z 425 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.74 (1H, s); 9.89 (1H, s); 8.01 (1H, s); 7.37-7.33 (1H, m); 7.21-7.14 (1H, m); 7.08-7.03 (1H, m); 6.65 (1H, dd, *J*=1.89, 8.04 Hz); 4.49-4.42 (1H, m); 3.51, 3.34 (1H each, ABq, *J*=14.73 Hz); 3.39-3.28 (2H, m); 3.18-3.08 (2H, m); 2.02 (3H, s); 2.00-1.92 (2H, m); 1.76-1.65 (2H, m); 1.33 (3H, s).

(5S)-5-[4-(4-Chloro-benzoyl)-piperazine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 415 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.75 (1H, s); 8.04 (1H, s); 7.54 (2H, d, *J*=8.38 Hz); 7.45 (2H, d, *J*=8.38 Hz); 3.79-3.55 (2H, bs); 3.56, 3.35 (1H each, ABq, *J*=14.84 Hz); 3.51-3.31 (2H, bs); 3.27-3.06 (4H, bs); 1.33 (3H, s).

1-((4S)-4-Methyl-2,5-dioxo-imidazolidine-4-ylmethanesulfonyl)-piperidine-4-carboxylic acid (4-fluoro-phenyl)-amide

LC-MS (APCI) m/z 413 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.74 (1H, s); 9.97 (1H, s); 8.02 (1H, s); 7.65-7.58 (2H, m); 7.16-7.09 (2H, m); 3.62-3.52 (2H, m); 3.49, 3.33 (1H each, ABq, *J*=14.94 Hz); 2.87-2.77 (2H, m); 2.48-2.39 (1H, m); 1.91-1.84 (2H, m); 1.70-1.57 (2H, m); 1.33 (3H, s).

(5S)-5-[4-(5-Bromo-pyridin-2-yloxy)-piperidine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 447, 449 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.73 (1H, s); 8.28 (1H, d, *J*=2.64 Hz); 8.01 (1H, s); 7.91 (1H, dd, *J*=2.60, 8.84 Hz); 6.83 (1H, d, *J*=8.79 Hz); 5.12-5.05 (1H, m); 3.52, 3.35 (1H each, ABq,

J=14.85 Hz); 3.41-3.34 (2H, m); 3.17-3.08 (2H, m); 2.06-1.97 (2H, m); 1.78-1.67 (2H, m); 1.33 (3H, s).

(5S)-5-[4-(5-(4-Fluoro-phenyl)-pyridin-2-yl)-piperazine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 448 (MH+).

^{1}H NMR (DMSO-d_6): δ 10.75 (1H, s); 8.45 (1H, d, *J*=2.51 Hz); 8.02 (1H, s); 7.88 (1H, dd, *J*=2.57, 8.86 Hz); 7.70-7.62 (2H, m); 7.30-7.22 (2H, m); 6.98 (1H, d, *J*=8.94 Hz); 3.70-3.62 (4H, m); 3.55, 3.36 (1 H each, ABq, *J*=14.73 Hz); 3.26-3.19 (4H, m); 1.32 (3H, s)

(5S)-5-[4-(5-(4-Methoxy-phenyl)-pyridin-2-yl)-piperazine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 460 (MH+).

(5S)-5-[4-(5-(4-Chloro-phenyl)-pyridin-2-yl)-piperazine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 464, 466 (MH+).

(5S)-5-[4-(5-(4-Trifluoromethoxy-phenyl)-pyridin-2-yl)-piperazine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 514 (MH+).

(5S)-5-[4-(5-Furan-2-yl-pyridin-2-yl)-piperazine-1-sulfonylmethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 420 (MH+).

(5S)-5-Methyl-5-(4-[5-(1*H*-pyrrol-2-yl)-pyridine-2-yl]-piperazine-1-sulfonylmethyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 419 (MH+).

(5S)-5-(4-[3,3']-Bipyridinyl-6-yl-piperazine-1-sulfonylmethyl)-5-methyl-imidazolidine-2,4-dione

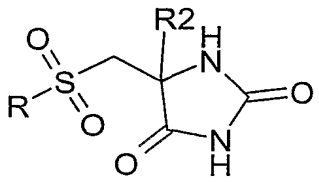
LC-MS (APCI) m/z 431 (MH+).

(4S)-4-(6-[4-(4-Methyl-2,5-dioxo-imidazolidin-4-ylmethanesulfonyl)-piperazine-1-yl]-pyridine-3-yl)-benzonitrile

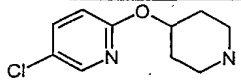
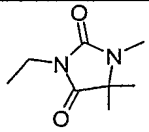
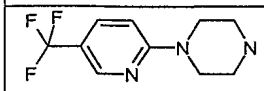
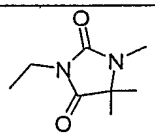
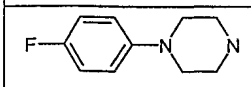
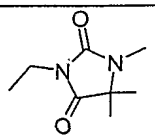
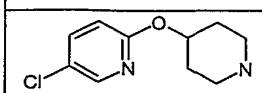
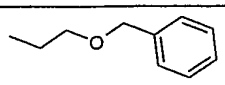
LC-MS (APCI) m/z 455 (MH+).

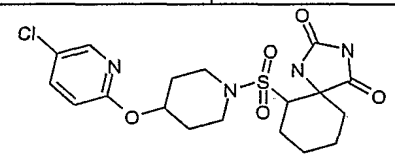
EXAMPLE 19

Compounds with the general formula



were synthesised according to the method described in Example 17.

R	R2	Analysis
		m/z 543 (MH+)[1]
		m/z 562 (MH+)[1]
		m/z 511(MH+)[1]
		m/z 523 (MH+)[1]

R	R2	Analysis
		m/z 443 (MH+)[1]

[1] : NMR available, see experimental part.

5-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-5-[(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)methyl]imidazolidine-2,4-dione

The title compound was prepared as described in Example17 from racemic {2,5-dioxo-4-[(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)methyl]imidazolidin-4-yl}methanesulfonyl chloride and 5-chloro-2-(piperidin-4-yloxy)-pyridine.

LC-MS (APCI) m/z 543 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.28 (6H, s); 1.63-1.74 (2H, m); 1.95-2.05 (2H, m); 2.77 (3H, s); 3.14 (4H, d); 3.53-3.73 (3H, m); 4.14 (1H, q); 5.04-5.11 (1H, m); 6.85 (1H, d); 7.80 (1H, dd); 7.94 (1H, s); 8.19 (1H, d); 10.83 (1H, s).

The startingmaterial was prepared as follows:

3-[3-(benzylthio)-2-oxopropyl]-1,5,5-trimethylimidazolidine-2,4-dione

Benzyl mercaptan (256 µl, 2.2 mmol) was stirred with cesium carbonate (712 mg, 2.2 mmol) in dimethyl formamide (5 ml) at room temperature for 1 hour. 3-(3-bromo-2-oxopropyl)-1,5,5-trimethylimidazolidine-2,4-dione (552 mg, 1.99 mmol) prepared as in W099/06361 was added and the mixture stirred 18 hours at room temperature. The reaction mixture was treated with water, extracted into ethyl acetate (3 x 25 ml), the organic phases combined, brine washed and dried. The product was purified by silica chromatography, eluting with 50% ethyl acetate / iso-hexane to give 300 mg product.

LC-MS (APCI) m/z 321 (MH+).

^{1}H NMR ($CDCl_3$): δ 1.45 (6H, s); 2.91 (3H, s); 3.16 (2H, s); 3.70 (2H, s); 4.53 (2H, s); 7.22-7.33 (5H, m).

5-[(benzylthio)methyl]-5-[(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)methyl]imidazolidine-2,4-dione

The title compound was prepared as described in the synthesis of 5-methyl-5-{[(phenylmethyl)thio]methyl} imidazolidine-2,4-dione in Example 17.

LC-MS (APCI) m/z 391 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.28 (6H, s); 2.64 and 2.76 (2H, abq, *J*=14.2 Hz); 2.78 (3H, s); 3.54 & 3.64 (2H, abq, *J*=14.2 Hz); 3.73 (2H, s); 7.20-7.32 (5H, m); 7.98 (1H, s); 10.83 (1H, s).

{2,5-dioxo-4-[(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)methyl]imidazolidin-4-yl}methanesulfonyl chloride

The title compound was prepared as described in the synthesis of [(4*S*) and (4R)-4-methyl-2,5-dioxoimidazolidin-4-yl]methanesulfonyl chloride in Example 17.

^{1}H NMR (CD_3OD): δ 1.38 (6H, s); 2.89 (3H, s); 3.81 and 3.92 (2H, abq, *J*=14.3 Hz); 4.61 (2H, s).

The following compounds were prepared as described in the synthesis of 5-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-5-[(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)methyl]imidazolidine-2,4-dione.

5-[({4-[5-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}sulfonyl)methyl]-5-[(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)methyl]imidazolidine-2,4-dione

LC-MS (APCI) m/z 562 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.26 (6H, s); 2.76 (3H, s); 3.16-3.22 (4H, m); 3.48-3.76 (8H, m); 7.02 (1H, d); 7.81-7.76 (2H, m); 8.43 (1H, s); 10.83 (1H, s).

5-[4-(4-Fluoro-phenyl-piperazine-1-sulfonylmethyl]-5-[(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)methyl]imidazolidine-2,4-dione

LC-MS (APCI) m/z 511 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.28 (6H, s); 2.77 (3H, s); 3.10-3.16 (4H, m); 3.21-3.26 (4H, m); 3.48-3.71 (4H, m); 6.95-7.09 (4H, m); 7.88 (1H, s); 10.84 (1H, bs).

5-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-5-{2-[(phenylmethyl)oxy]ethyl}imidazolidine-2,4-dione

The title compound was prepared as described in the synthesis of 5-[({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)methyl]-5-[(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)methyl]imidazolidine-2,4-dione starting from 5-Chloro-2-(piperidine-4-yloxy)-pyridine hydrochloride and (2,5-dioxo-4-{2-[(phenylmethyl)oxy]ethyl}imidazolidin-4-yl)methanesulfonyl chloride.

LC-MS (APCI) m/z 523 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.37-1.79 (3H, m); 1.83-2.08 (4H, m); 3.00-3.56 (7H, m partially obscured by D_2O); 4.33-4.44 (2H, m); 5.01-5.12 (1H, m); 6.85 (1H, d); 7.21-7.36 (5H, m); 7.80 (1H, dd); 8.02 (1H, s); 8.19 (1H, d); 10.70 (1H, bs).

6-({4-[(5-chloropyridin-2-yl)oxy]piperidin-1-yl}sulfonyl)-1,3-diazaspiro[4.5]decane-2,4-dione

LC-MS (APCI) m/z 443 (MH+).

The startingmaterial was prepared as follows:

6-[(phenylmethyl)thio]-1,3-diazaspiro[4.5]decane-2,4-dione

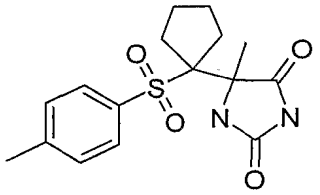
Benzylmercaptan (937mg, 7.5mmol) was dissolved in 70 mL of THF. NaH (362mg 60%, 9.0mmol) was added and the slurry was stirred for some minutes. 2-chlorocyclohexanone (1.0g, 7.5mmol) was added and the reaction was stirred at rt over night. The solid was filtered of and the solvent was removed by rotary evaporation. Potassium cyanid (4 eq),

$(NH4)_2CO_3$ (8eq) and 25mL of ethanol was added. The reaction was stirred in a sealed vial at 80°C over night. The suspension was filtered and the solid was recrystallised from DMSO and water to give the title compound as a white solid

LC-MS (APCI) m/z 291 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.21-1.81 (8H, m); 2.79 (1H, dd); 3.67-3.76 (2H, m); 7.18-7.32 (5H, m); 8.43 (1H, s); 10.68 (1H, s).

EXAMPLE 20



5-Methyl-5-(1-(toluene-4-sulfonyl)-cyclopentyl)-imidazolidine-2,4-dione

1-(1-(Toluene-4-sulfonyl)-cyclopentyl))-ethanone (0.10 g, 0.38 mmol), potassium cyanide (0.049 g, 0.75 mmol), ammonium carbonate (0.18 g, 1.9 mmol), 50% ethanol in water (1.6 mL) were stirred in a sealed tube (2 mL volume) at 90°C for 70 hours. The solution was acidified with 10% acetic acid to pH 6 and concentrated by rotary evaporation to half of its original volume upon which part of the product fell out. The solution and its solid contents were taken up in ethyl acetate, the aqueous phase was separated and washed twice with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated by rotary evaporation to give 0.74 g of a white solid. The crude product was dissolved in methanol (5 mL), concentrated with silica (1 g) by rotary evaporation and applied on a short silica column. Elution with ethyl acetate/ n-heptane (1:2 and 2:1) gave 0.060 g (48%) of the title product as colourless needles.

LC-MS (APCI) m/z 337 (MH+).

^{1}H NMR (DMSO-d_6): δ 0.96-1.10 (1H, m); 1.32-1.44 (1H, m); 1.36 (3H, s); 1.47-1.58 (2H, m); 2.10-2.30 (4H, m); 2.40 (3H, s); 7.41 (2H, d, J= 8 Hz); 7.72 (2H, d, J= 8 Hz); 7.80 (1H, bs) and 10.7 (1H, bs).

^{13}C NMR (DMSO-d_6): δ 21.0, 22.60, 22.64, 26.1, 26.3, 30.8, 31.5, 64.1, 78.9, 129.2, 130.3, 135.3, 144.2, 156.0 and 176.2.

The starting material was prepared as follows:

1-(Toluene-4-sulfonyl)-propan-2-one

was prepared according to Crandall et al. J. Org. Chem. 1985, (8) 50, 1327-1329 from sodium *p*-toluensulfinate dihydrate (4.2 g, 18 mmol), chloroacetone (1.0 mL, 12 mmol), n-tetrabutylammonium bromide (0.30 g) and water-benzene-acetone 4:3:3 (10 mL). Work-up and chromatography on silica of the crude using ethyl acetate/ n-heptane (1:3 through 1:2) as eluent gave 2.4 g (95%) of the title product as an oil which crystallised on standing in the fridge.

LC-MS (APCI) m/z 213 (MH+).

^{1}H NMR ($CDCl_3$): δ 2.38 (3H, s); 2.42 (3H, s); 4.10 (2H, s); 7.35 (d2H, d, *J*= 8 Hz); 7.74 (d, 2 H, d, *J*= 8 Hz).

^{13}C NMR ($CDCl_3$): δ 21.7, 31.4, 67.7, 128.0, 129.8, 135.5, 145.3 and 195.9.

1-(1-(Toluene-4-sulfonyl)-cyclopentyl))-ethanone

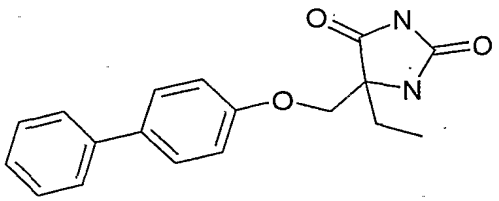
1-(Toluene-4-sulfonyl)-propan-2-one (0.10 g, 0.47 mmol), 1,4-diiodobutane (0.068 mL, 0.52 mmol), finely ground potassium carbonate (0.14 g, 1.0 mmol) and dry dimethylsulfoxide (0.80 mL) were stirred at 50°C (oil bath temperature) for 22 hours. The heating was shut off and stirring was continued at 22°C for 22 hours. The crude product was taken up in ethyl acetate, washed with water (5x 50 mL) and brine (1x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated by rotary evaporation. The oily residue was chromatographed on silica using ethyl acetate/ n-heptane (1:4 through 1:3) to give 0.10 g (80%) of the title product as a colourless oil.

LC-MS (APCI) m/z 267 (MH+).

^{1}H NMR ($CDCl_3$): δ 1.52 (2H, m); 1.77 (2H, m); 2.26 (2H, m); 2.37 (2H, m); 2.42 (3H, s); 2.48 (3H, s); 7.30 (2H, d, *J*= 8 Hz) and 7.60 (2H, d, *J*= 8 Hz).

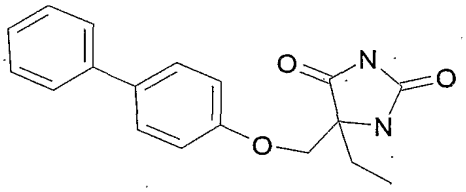
^{13}C NMR ($CDCl_3$): δ 21.7, 25.4, 28.0, 31.3, 83.9, 129.4, 129.5, 133.2, 145.0 and 202.5.

EXAMPLE 21



5-(Biphenyl-4-yloxymethyl)-5-ethyl-imidazolidine-2,4-dione

4-Hydroxy-biphenyl (84 mg, 0.5 mmol) was added to 1-bromo-2-butanone (0.055 ml, 0.55 mmol) and anhydrous potassium carbonate (95 mg, 0.69 mmol) in dry aceton (2.5 ml). The



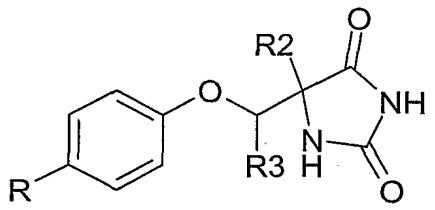
mixture was stirred for 2 hours at ambidient temperature, then diluted with ethylacetate (2.5 ml). The supernantant was evaporated. The afforded oil was stirred at 75 °C overnight, in a sealed vial, together with ammonium carbonate (290 mg, 3.0 mmol) and potassium cyanide (79 mg, 1.2 mmol) in 50 % ethanol (3 ml). The resulting solution was pured out on ethylacetate (20 ml), ether (10 ml) and water (15 ml), together with saturated ammonium chloride (aq, 2 ml). The organic phase was washed additionally once with water (10 ml), then evaporated together with heptane to afford the title compound (112 mg, 0.36 mmol) as a white solid in 72 % yield.

^{1}HNMR (300 MHz, DMSO-d_6): δ 10.57 (1H, bs); 8.00 (1H, s); 7.63-7.58 (4H, m); 7.43 (2H, m); 7.01 (2H, d); 4.07 (2H, dd); 1.67 (2H, m); 0.86 (3H, t).

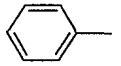
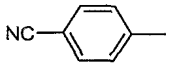
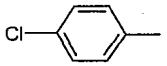
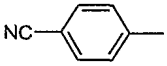
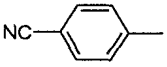
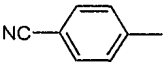
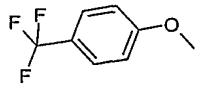
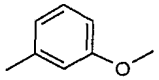
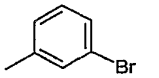
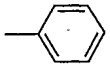
LC-MS (APCI) m/z 311.1 (MH+).

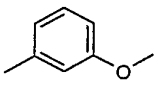
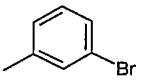
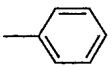
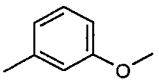
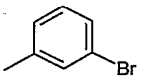
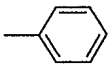
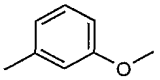
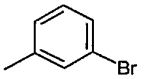
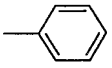
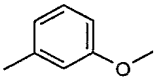
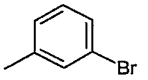
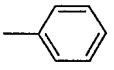
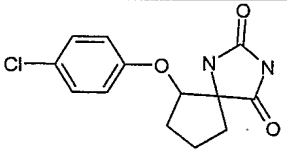
EXAMPLE 22

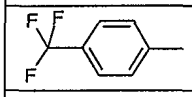
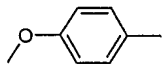
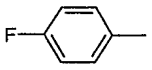
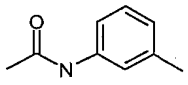
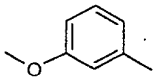
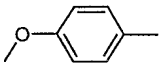
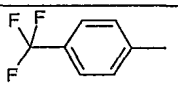
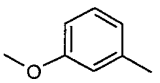
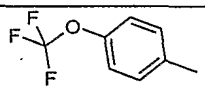
Compounds with the general formula



were synthesised according to the method described in Example 21

R	R2	R3	Analysis
	Me	Me	m/z 311 (MH+)
	Et	H	m/z 336 (MH+)
	Me	H	m/z 331 (MH+)
	Me	H	m/z 322 (MH+)
	tBu	H	m/z 364 (MH+)
	Ph	H	m/z 384 (MH+)
	Me	H	m/z 381 (MH+)
CN		H	m/z 338 (MH+)
CN		H	m/z 386 (MH+)
CN		H	m/z 308 (MH+)

R	R2	R3	Analysis
Br		H	m/z 393 (MH+)
Br		H	m/z 443 (MH+)
Br		H	m/z 363 (MH+)
OMe		H	m/z 343 (MH+)
OMe		H	m/z 393(MH+)
OMe		H	m/z 313 (MH+)
Me		H	m/z 327 (MH+)
Me		H	m/z 377 (MH+)
Me		H	m/z 297 (MH+)
H		H	m/z 313 (MH+)
H		H	m/z 363 (MH+)
H		H	m/z 283 (MH+)
			m/z 281 (MH+)
	Me	H	m/z 303 (MH+)[1]

R	R2	R3	Analysis
	Me	H	m/z 365 (MH+)[1]
	Me	H	m/z 326 (MH+)
	Me	H	m/z 315 (MH+)[1]
	Me	H	m/z 354 (MH+)[1]
	Me	H	m/z 327 (MH+)[1]
	Et	H	m/z 341(MH+)[1]
	Et	H	m/z 378 (MH+)[1]
	Et	H	m/z 340 (MH+)[1]
	Et	H	m/z 395 (MH+)[1]
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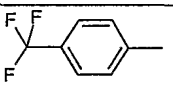
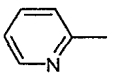
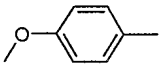
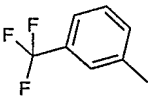
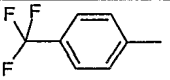
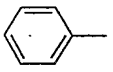
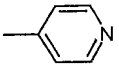
	Ph	H	m/z 426 (MH+)[1]
	tBu	H	m/z 340 (MH+)[1]
	tBu	H	m/z 368 (MH+)[1]
	tBu	H	m/z 406 (MH+)[1]
	tBu	H	m/z 407 (MH+)[1]
		H	m/z 360 (MH+)[1]

[1]: For NMR-data see experimental part.

5-[1-(Biphenyl-4-yloxy)-ethyl]-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 311.2 (MH+).

5-(4'-Cyano-biphenyl-4-yloxymethyl)-5-ethyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 336.2 (MH+).

5-(4'-Chloro-biphenyl-4-yloxymethyl)-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 331.2 (MH+).

5-(4'-Cyano-biphenyl-4-yloxymethyl)-5-methyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 322.2 (MH+).

5-(4'-Cyano-biphenyl-4-yloxymethyl)-5-tert-butyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 364 (MH+).

5-(4'-Cyano-biphenyl-4-yloxymethyl)-5-phenyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 384 (MH+).

5-Methyl-5-[4-(4-trifluoromethyl-phenoxy)-phenoxymethyl]-imidazolidine-2,4-dione

LC-MS (APCI) m/z 381.4 (MH+).

5-(4-Cyano-phenoxymethyl)-5-(3-methoxy-phenyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 338.2 (MH+).

5-(4-Cyano-phenoxymethyl)-5-(3-bromo-phenyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 386.1 (MH+).

5-(4-Cyano-phenoxymethyl)-5-phenyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 308.1 (MH+).

5-(4-Bromo-phenoxymethyl)-5-(3-methoxy-phenyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 393.1 (MH+).

5-(4-Bromo-phenoxymethyl)-5-(3-bromo-phenyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 442.9 (MH+).

5-(4-Bromo-phenoxymethyl)-5-phenyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 363.1 (MH+).

5-(4-Methoxy-phenoxymethyl)-5-(3-methoxy-phenyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 343.2(MH+).

5-(4-Methoxy-phenoxymethyl)-5-(3-bromo-phenyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 393.2 (MH+).

5-(4-Methoxy-phenoxymethyl)-5-phenyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 313.2 (MH+).

5-(4-Methyl-phenoxymethyl)-5-(3-methoxy-phenyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 327.1 (MH+).

5-(4-Methyl-phenoxymethyl)-5-(3-bromo-phenyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 377.1 (MH+).

5-(4-Methyl-phenoxymethyl)-5-phenyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 297.1 (MH+).

5-Phenoxymethyl-5-(3-methoxy-phenyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 313.2 (MH+).

5-Phenoxymethyl-5-(3-bromo-phenyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 363 (MH+).

5-Phenoxymethyl-5-phenyl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 283.2 (MH+).

6-(4-Chloro-phenoxy)-1,3-diaza-spiro[4,4]nonane-2,4-dione

LC-MS (APCI) m/z 281 (MH+).

5-Methyl-5-[(4-thiophen-2-yl-phenoxymethyl)-imidazolidine-2,4-dione

1-(4-Thien-2-ylphenoxy)acetone (114 mg, 0.49 mmol), sodium cyanide (40 mg, 0.81 mmol), ammonium carbonate (222 mg, 2.85 mmol) water (5 ml) and ethanol were mixed and heated at 80 °C for 10 hours. After cooling the reaction mixture was treated with water, the solid was filtered off and dried to give 105 mg product.

LC-MS (APCI) m/z 303 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.31 (3H, s); 3.95, 4.10 (2H, abq, *J*=9.8 Hz); 6.95 (2H, d); 7.08 (1H, dd); 7.37 (1H, d); 7.45 (1H, d); 7.55 (2H, d); 8.03 (1H, s).

The startingmaterials were prepared as follows:

1-(4-Iodophenoxy)acetone

4-Iodophenol (4.9g, 22 mmol) was stirred together with potassium carbonate (4.7 g, 33 mmol), chloroacetone (4.5 ml, 55 mmol) and acetone at reflux for 18 hours. The reaction mixture was poured into water (100 mL), extracted with ethyl acetate (3 x 50 mL), the

extracts were brine washed, dried over sodium sulphate and evaporated. The residue was purified by flash chromatography eluting with dichloromethane.

LC-MS (APCI) m/z 275 (MH+).

^{1}H NMR ($CDCl_3$): δ 2.26 (3H, s); 4.51 (2H, s); 6.65 (2H, d); 7.57 (2H, d).

1-(4-Thien-2-ylphenoxy)acetone

1-(4-Iodophenoxy)acetone (192 mg, 0.69 mmol) was treated with thiophen-2-boronic acid (102 mg, 0.79 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloro palladium (II) complex with dichloromethane (1:1) (36 mg), dimethylformamide (12 mL) and ammonium acetate (135 mg) were stirred together at 80 °C for 3 hours. After cooling the reaction mixture was treated with dilute hydrochloric acid and extracted into ethyl acetate. The product was purified by flash chromatography on silica, eluting with 50 % ethyl acetate : iso-hexane to give 114 mg product.

LC-MS (APCI) m/z 232 (MH+).

The following compounds were prepared as described in the synthesis of 5-methyl-5-[(4-thien-2-ylphenoxy)methyl]imidazolidine-2,4-dione

5-Methyl-5-(4'-(trifluoromethyl-biphenyl-4-yloxymethyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 365 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.46 (3H, s); 4.05, 4.22 (2H, ABq, *J*=9.9 Hz); 7.04 (2H, d); 7.61 (2H, d); 7.04, 7.61 (4H, ABq, *J*=9.8 Hz).

5-(4'-(Methoxy-biphenyl-4-yloxymethyl)- 5-methyl -imidazolidine-2,4-dione

LC-MS (APCI) m/z 326 (MH+).

5-(4'-(Fluoro-biphenyl-4-yloxymethyl)- 5-methyl -imidazolidine-2,4-dione

LC-MS (APCI) m/z 315 (MH+).

^{1}H NMR (DMSO-d_6): δ 1,45 (3H, s); 4.02, 4.20 (2H, abq, *J*=9.9 Hz); 6.99 (2H, d); 7.12

(2H, t); 7.50 (2H, d); 7.55 (2H, dd).

N-[4'-(4-Methyl-2,5-dioxo-imidazolidin-4-ylmethoxy)-biphenyl-3-yl]-acetamide

LC-MS (APCI) m/z 354 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.46 (3H, s); 2.14 (3H, s); 2.15 (1H, s); 4.05, 4.20 (2H, abq, *J*=9.6 Hz); 7.00 (2H, d); 7.28-7.40 (3H, m); 7.46 (1H, bd); 7.53 (2H, d); 7.78-7.81 (1H, m).

5-(3'-(Methoxy-biphenyl-4-yloxymethyl)- 5-methyl -imidazolidine-2,4-dione

LC-MS (APCI) m/z 327 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.45 (3H, s); 3.83 (3H, s); 4.04, 4.20 (2H, abq, *J*=9.6 Hz); 6.85 (1H, dd); 6.99 (2H, d); 7.08 (1H, m); 7.12 (1H, d); 7.30 (1H, t); 7.53 (2H, d).

5-Ethyl-5-(4'-(methoxy-biphenyl-4-yloxymethyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 341 (MH+).

^{1}H NMR (DMSO-d_6): δ 0.48 (3H, t); 1.56-1.74 (2H, m); 3.77 (3H, s); 3.97, 4.11 (2H, abq, *J*=10.0 Hz); 6.94-7.00 (4H, m); 7.49-7.54 (4H, m); 7.97 (1H, s); 10.71 (1H, brs)

5-Ethyl-5-(4'-(trifluoromethyl-biphenyl-4-yloxymethyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 378 (MH+).

^{1}H NMR (DMSO-d_6): δ 0.83 (3H, t); 1.66 (2H, oct); 4.01, 4.14 (2H, abq, *J*=9.8 Hz); 7.04 (2H, d); 7.67 (2H, d); 7.75 (2H, d); 7.84 (2H, d); 8.01 (1H, s); 10.75 (1H, bs).

5-Ethyl-5-(3'-(methoxy-biphenyl-4-yloxymethyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 340 (MH+).

^{1}H NMR (DMSO-d_6): δ 0.83 (3H, t); 1.65 (2H, oct); 3.76 (3H, s); 3.97, 4.10 (2H, abq, *J*=9.7 Hz); 6.93-6.99 (3H, m); 7.49-7.53 (3H, m); 7.99 (1H, s); 10.74 (1H, bs).

5-Ethyl-5-(4'-(trifluoromethoxy-biphenyl-4-yloxymethyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 395 (MH+).

^{1}H NMR (DMSO-d_6): δ 0.84 (3H, t); 1.56-1.74 (2H, m); 4.00, 4.13 (2H, abq, *J*=10.9 Hz); 7.01 (2H, d); 7.40 (2H, d); 7.61, 7.72 (4H, abq, *J*=8.9 Hz); 7.79 (1H, s); 10.72 (1H, bs).

5-Ethyl-5-[(4-thiophen-2-yl-phenoxymethyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 317 (MH+).

^{1}H NMR (DMSO-d_6): δ 0.82 (3H, t); 1.54-1.74 (2H, m); 3.97, 4.12 (2H, abq, *J*=10.0 Hz); 6.95 (2H, d); 7.08 (1H, dd); 7.37 (1H, dd); 7.44 (1H, dd); 7.55 (2H, d); 7.98 (1H, s); 10.67 (1H, s).

5-Phenyl-5-(4'-(trifluoromethyl-biphenyl-4-yloxymethyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 426 (MH+).

^{1}H NMR (DMSO-d_6): δ 4.21, 4.62 (2H, abq, *J*=10.1 Hz); 7.10 (2H, d); 7.38-7.47 (3H, m); 7.61-7.69 (4H, m); 7.76, 7.84 (4H, abq, *J*=8.8 Hz); 8.76 (1H, s); 10.92 (1H, bs).

5-*tert*-Butyl-5-(4-pyridin-3-yl-phenoxymethyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 340 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.02 (9H, s); 4.15, 4.36 (2H, abq, *J*=9.9 Hz); 7.10 (2H, d); 7.70-7.75 (3H, m); 8.08 (1H, s); 8.39 (1H, dd); 8.65 (1H, dd); 9.00 (1H, s).

5-*tert* -Butyl-5-(4'-methoxy-biphenyl-4-yloxymethyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 368 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.01 (9H, s); 3.76 (3H, s); 4.10, 4.31 (2H, abq, *J*=9.7 Hz); 6.95-7.01 (4H, dd); 7.48-7.55 (4H, dd); 8.05 (1H, s); 10.59 (1H, bs).

5-*tert* -Butyl-5-(3'-trifluoromethyl-biphenyl-4-yloxymethyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 406 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.01 (9H, s); 4.14, 4.35 (2H, abq, *J*=9.6 Hz); 7.06 (2H, d); 7.65-7.69 (4H, m); 7.89 (1H, s); 7.93 (1H, t); 8.08 (1H, s); 10.65 (1H, s).

5-*tert* -Butyl-5-(4'-trifluoromethyl-biphenyl-4-yloxymethyl)-imidazolidine-2,4-dione

LC-MS (APCI) m/z 407 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.03 (9H, s); 4.15, 4.36 (2H, abq, J=10.0 Hz); 7.07, 7.68 (4H, abq, *J*=8.9 Hz); 7.76, 7.84 (4H, abq, *J*=8.9 Hz); 8.08 (1H, s); 10.67 (1H, s).

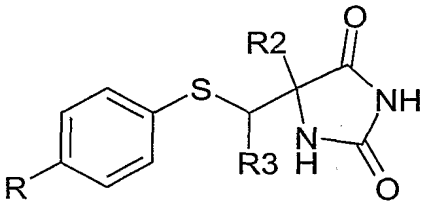
5-(Biphenyl-4-yloxymethyl)-5-pyridin-4-yl-imidazolidine-2,4-dione

LC-MS (APCI) m/z 360 (MH+).

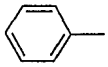
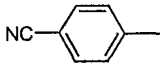
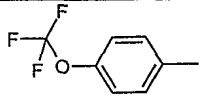
^{1}H NMR (CD_3OD): δ 4.41, 4.71 (2H, ABq, *J*=9.7 Hz); 7.02 (2H, d); 7.28 (1H, t); 7.39 (2H, t); 7.55 (2H, d); 8.14 (2H, d); 8.81 (2H, d).

EXAMPLE 23

Compounds with the general formula



were synthesised according to the method described in Example 21

R	R2	Analysis (1)
	Me	m/z 313 (MH+)
	Me	-
	Me	m/z 397 (MH+)

(1): For NMR-data see experimental part.

5-[(1,1'-biphenyl-4-ylthio)methyl]-5-methylimidazolidine-2,4-dione

LC-MS(APCI) m/z 313 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.36 (3H, s); 3.28 (2H, s); 7.34 (1H, t); 7.44 (4H, t); 7.60 (2H, d); 7.64 (2H, d); 7.97 (1H, s); 10.74 (1H, bs).

The startingmaterial was prepared as follows:

1-(1,1'-biphenyl-4-ylthio)propan-2-one

1-[(4-bromophenyl)thio]propan-2-one (357 mg, 1.46 mmol) was treated with phenyl boronic acid (231 mg, 1.89 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloro palladium (II) complex with dichloromethane (1:1) (36 mg), toluene (20 ml), methanol (7.5 ml), saturated sodium carbonate solution (3.5 ml) and were stirred together at 80 °C for 18 hours. After cooling the reaction mixture was treated with dilute hydrochloric acid and extracted into ethyl acetate. The product was purified by flash chromatography on silica, eluting with 25 % ethyl acetate : iso-hexane to give 277 mg product.

GC/MS m/z: 242 [M^+].

^{1}H NMR ($CDCl_3$): δ 2.33 (3H, s); 3.73 (2H, s); 7.37 (1H, s); 7.42-7.48 (4H, m); 7.54-7.59 (4H, m).

The following compounds were prepared as described in the synthesis of 5-[(1,1'-biphenyl-4-ylthio)methyl]-5-methylimidazolidine-2,4-dione

4'-{[(4-methyl-2,5-dioxoimidazolidin-4-yl)methyl]thio}-1,1'-biphenyl-4-carbonitrile

The starting material, 4'-[(2-oxopropyl)thio]-1,1'-biphenyl-4-carbonitrile, was prepared as described in the synthesis of 1-(1,1'-biphenyl-4-ylthio)propan-2-one.

^{1}H NMR (DMSO-d_6): δ 1.37 (3H, s); 3.30 (2H, s); 7.45, 7.67 (4H, abq, *J*=7.5 Hz); 7.88 (4H, q); 7.99 (1H, s); 10.75 (1H, bs).

5-methyl-5-[({4'-[(trifluoromethyl)oxy]-1,1'-biphenyl-4-yl}thio)methyl]imidazolidine-2,4-dione

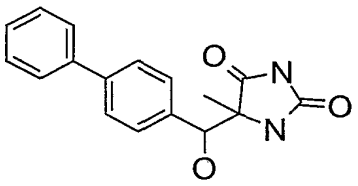
The starting material, 1-({4'-[(trifluoromethyl)oxy]-1,1'-biphenyl-4-yl}thio)propan-2-one, was prepared as described in the synthesis of 1-(1,1'-biphenyl-4-ylthio)propan-2-one.

LC-MS(APCI) m/z very weak 397 (MH+).

^{1}H NMR (DMSO-d_6): δ 1.33 (3H, s); 3.29 (2H, s); 7.42-7.45 (4H, m); 7.61 (2H, d); 7.77 (2H, d); 7.99 (1H, s); 10.75 (1H, s).

EXAMPLE 24

5-(Biphenyl-4-yl-hydroxy-methyl)-5-methyl-imidazolidine-2,4-dione



4-Biphenylcarboxaldehyde (182 mg, 1.0 mmol) and trimethylamine (45% in water, 160 µl, 1.0 mmol) was added to a warm solution of 5-methyl-imidazolidine-2,4-dione (114 mg, 1.0 mmol) in methanol (4.0 ml) and water (1.0 ml). The reaction was heated to reflux for 16 hours with nitrogen as inert atmosphere.

The solution was cooled, evaporated and stirred in a 100/1 mixture of dichloromethane/methanol (15 ml). Filtration, washing of the precipitate with the same solvent mixture (10 ml), and drying by airsuction, afforded 5-(Biphenyl-4-yl-hydroxy-methyl)-imidazolidine-2,4-dione (190 mg) in 64.1 % yield as a diasteromeric mixture of 60/40 according to HNMR.

The isomeric mixture (180 mg) was dissolved in dioxane (8 ml) and water (4 ml). Preparative HPLC on a Chromasil C18 250/20 mm column (KR-100-5-C18), with a gradient of acetonitril/water (0.1 % trifluoroacetic acid), from 20/80 to 40/60 during 25 min, afforded the two isolated diasteromeres in 43.5 % total yield.

A preliminary stereostructural determination was done for each isomer by comparing the HNMR with the two diastereomeres of 5-[(4-chloro-phenyl)-hydroxy-methyl)]-imidazolidine-2,4-dione, of which both diasteromeric structures had been determined earlier by different NMR experiments in detail. The shift for the 1-NH proton and the phenyl attached to the imidazolelidione was especially indicative in this diastereomeric assignment.

(RR)-5-(Biphenyl-4-yl-hydroxy-(SS)-methyl)-5-methyl-imidazolidine-2,4-dione

1H NMR (400 MHz, DMSO-d6): 10.19 (1H, s); 8.11 (1H, s); 7.66 (2H, d, J = 7.61Hz); 7.59 (2H, d, J = 8.20 Hz); 7.45 (2H, t, J = 7.68 Hz); 7.37 (2H, d, J = 8.27 Hz); 7.35 (1H, t, J = 7.62 Hz); 5.92 (1H, bs); 4.67 (1H, s); 1.44 (3H, s).

13C NMR (400 MHz, DMSO-d6): 176.79; 156.25; 139.74; 139.39; 139.14; 128.91; 128.20; 127.37; 126.51; 125.54; 75.32; 66.96; 21.22.

APCI-MS m/z: 297.3 [MH+].

(SR)-5-(Biphenyl-4-yl-hydroxy-(RS)-methyl)-5-methyl-imidazolidine-2,4-dione

1H NMR (400 MHz, DMSO-d6): 10.48 (1H, s); 7.67 (2H, d, J = 7.48 Hz); 7.64 (2H, d, J = 8.29 Hz); 7.56 (1H, s); 7.48-7.45 (4H, m); 7.36 (1H, t, J = 7.30 Hz); 5.75 (1H, d, J = 4.73 Hz); 4.65 (1H, d, J = 3.57 Hz); 1.08 (3H, s).

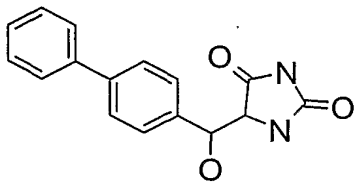
13C NMR (400 MHz, DMSO-d6): 177.89; 157.28; 139.88; 139.44; 139.27; 128.95; 128.47; 127.38; 126.54; 125.89; 74.68; 66.18; 20.22.

APCI-MS m/z: 297.3 [MH+].

The compounds described in Examples 25 to 27 were prepared using a method analogous to that given in Example 24.

EXAMPLE 25

(RR)-5-(Biphenyl-4-yl-hydroxy- (SS)-methyl)-imidazolidine-2, 4-dione



1H NMR (400 MHz, DMSO-d6): 10.33 (1H, s); 8.10 (1H, s); 7.66 (2H, d, J = 8.20 Hz); 7.61 (2H, d, J = 8.20 Hz); 7.45 (2H, dd, J = 8.20/7.20 Hz); 7.39 (2H, d, J = 8.24 Hz); 7.35 (1H, t, J = 7.48 Hz); 5.89 (1H, bs); 4.97 (1H, d, J = 2.5 Hz); 4.40 (1H, d, J = 2.5 Hz).

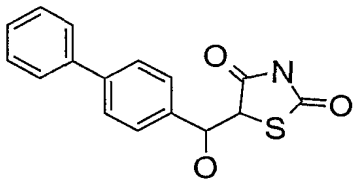
APCI-MS m/z: 283.1 [MH+].

(SR)-5-(Biphenyl-4-yl-hydroxy- (RS)-methyl)-imidazolidine-2, 4-dione

APCI-MS m/z: 283.1 [MH+].

EXAMPLE 26

5-(Biphenyl-4-yl-hydroxy-methyl)-thiazolelidine-2, 4-dione



(RR)-5-(Biphenyl-4-yl-hydroxy- (SS)-methyl)-thiazolelidine-2, 4-dione

1H NMR (400 MHz, DMSO-d6): 11.81 (1H, s); 7.68 (2H, d, J = 8.20 Hz); 7.64 (2H, d, J = 8.20 Hz); 7.46 (2H, dd, J = 8.30/7.50 Hz); 7.42 (2H, d, J = 8.30 Hz); 7.36 (1H, t, J = 7.50 Hz); 6.24 (1H, d, J = 3.96 Hz); 5.36 (1H, t, J = 3.95 Hz); 5.06 (1H, d, J = 4.03 Hz).

APCI-MS m/z: 183.1[MH+ - thiazolelidine-2, 4-dione].

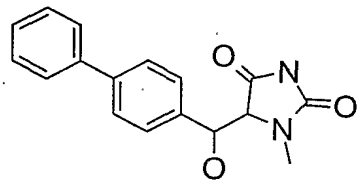
(SR)-5-(Biphenyl-4-yl-hydroxy- (RS)-methyl)-thiazolelidine-2, 4-dione

1H NMR (400 MHz, DMSO-d6): 12.04 (1H, s); 7.67 (2H, d, J = 8.30 Hz); 7.65 (2H, d, J = 8.30 Hz); 7.51 (2H, d, J = 8.20 Hz); 7.46 (2H, dd, J = 8.20/7.40 Hz); 7.36 (1H, t, J = 7.40 Hz); 6.22 (1H, d, J = 5.20 Hz); 5.42 (1H, dd, J = 5.20/2.60 Hz); 5.02 (1H, d, J = 2.60 Hz).

APCI-MS m/z: 183.1[MH+ - thiazolelidine-2, 4-dione].

EXAMPLE 27

5-(Biphenyl-4-yl-hydroxy-methyl)-1-methyl-imidazolidine-2, 4-dione



(RR)-5-(Biphenyl-4-yl-hydroxy- (SS)-methyl)-1-methyl-imidazolidine-2, 4-dione

1H NMR (400 MHz, DMSO-d6): 10.53 (1H, s); 7.67 (2H, d, J = 7.20 Hz); 7.63 (2H, d, J = 8.43 Hz); 7.46 (2H, dd, J = 7.71/7.20 Hz); 7.38 (2H, d, J = 8.63 Hz); 7.35 (1H, t, J = 7.63 Hz); 6.01(1H, d, J = 4.16 Hz); 5.13 (1H, dd, J = 4.18/2.60 Hz); 4.33 (1H, d, J = 2.58 Hz); 2.97 (3H, s).

13C NMR (400 MHz, DMSO-d6): 176.63; 156.83; 139.78; 138.97; 138.95; 128.89; 127.35; 127.13; 126.53; 125.91; 71.28; 67.81; 28.63.

APCI-MS m/z: 297.1 [MH+]

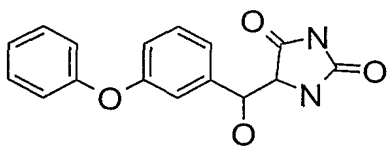
(SR)-5-(Biphenyl-4-yl-hydroxy- (RS)-methyl)-1-methyl-imidazolidine-2, 4-dione

1H NMR (400 MHz, DMSO-d6): 10.73 (1H, s); 7.70 (4H, m); 7.54 (2H, d, J = 8.22 Hz); 7.46 (2H, dd, J = 8.20/7.10 Hz); 7.36 (1H, t, J = 7.11 Hz); 5.96 (1H, d, J = 6.06 Hz); 5.11 (1H, dd, J =6.06/2.14 Hz); 4.38 (1H, d, J = 2.14 Hz); 2.33 (3H, s).

APCI-MS m/z: 297.1 [MH+]

EXAMPLE 28

5-[Hydroxy- (3-phenoxy-phenyl)-methyl]-imidazolidine-2, 4-dione



The compound was prepared according to the method given in Example 24 but instead of preparation by HPLC, flash chromatography (SiO, dichloromethane/methanol: gradient to

100/4) afforded 60 mg of the title compound as a white solid in 20.1 % yield (diastereomeric mixture). HNMR confirmed that the ratio of the mixture of the diastereomeric isomers was 1:1.

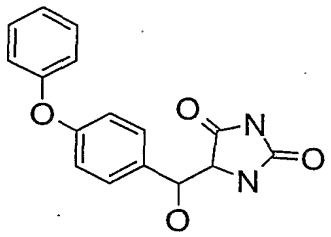
1H NMR (400 MHz, DMSO-d6): 10.51 (1H, bs); 10.37 (1H, bs); 8.04 (1H, s); 7.56 (1H, s); 7.40-7.29 (6H, m); 7.16-7.09 (4H, m); 7.05-7.02 (4H, m); 6.96 (2H, d, J = 8.71 Hz); 6.89 (2H, m); 5.89 (1H, d, J = 3.91 Hz); 5.78 (1H, d, J = 5.68 Hz); 4.93 - 4.90 (2H, m); 4.34 (1H,dd); 4.25 (1H, dd).

13C NMR (400 MHz, DMSO-d6): 174.04; 173.05; 158.09; 157.40; 156.89; 156.83; 156.31; 155.63; 144.01; 141.69; 129.96; 129.94; 129.55; 129.15; 123.20; 123.06; 122.26; 121.28; 118.44; 118.06; 118.02; 117.80; 117.46; 116.76; 71.98; 70.28; 64.01.

APCI-MS m/z: 281.1 [MH+ - H2O].

EXAMPLE 29

5-[Hydroxy- (4-phenoxy-phenyl)-methyl]-imidazolidine-2, 4-dione



The compound was prepared according to the method given in Example 24 but instead of preparation by HPLC, flash chromatography (SiO, dichloromethane/methanol: gradient to 100/3) afforded 40 mg of the title compound as a white solid in 13.4 % yield (diastereomeric mixture). HNMR confirmed that the ratio of the mixture of the diastereomeric isomers was 1:1.

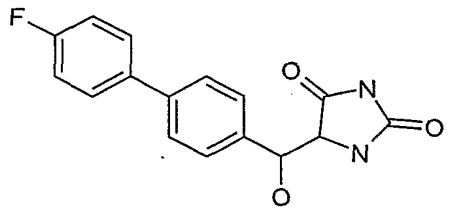
1H NMR (400 MHz, DMSO-d6): 10.49 (1H, bs); 10.36 (1H, bs); 8.04 (1H, s); 7.55 (1H, s); 7.41-7.35 (6H, m); 7.31 (2H, d, J = 8.60 Hz); 7.13 (2H, ddd, J = 7.44/3.52/1.14 Hz); 7.01 – 6.92 (8H, m); 5.84 (1H, d, J = 3.76 Hz); 5.74 (1H, d, J = 5.55 Hz); 4.91 (2H, m); 4.34 (1H,dd, J = 3.03/1.05 Hz); 4.22 (1H, DD, 2.68/1.52 Hz).

APCI-MS m/z: 281.1 [MH+ - H2O].

EXAMPLE 30

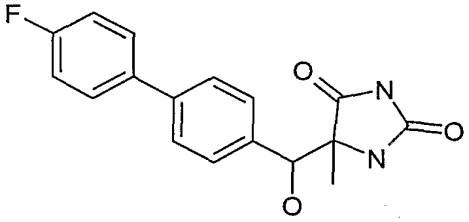
The following compounds were made according to the methods described for the Examples above.

5-[(4'-Fluoro-biphenyl-4-yl)-hydroxy-methyl]-imidazolidine-2,4-dione



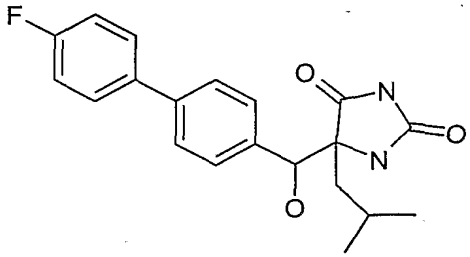
APCI-MS m/z: 283 [MH+ - H2O].

5-[(4'-Fluoro-biphenyl-4-yl)-hydroxy-methyl]-5-methyl-imidazolidine-2,4-dione



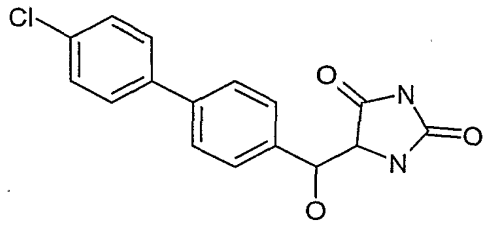
APCI-MS m/z: 314.9 [MH+].

5-[(4'-Fluoro-biphenyl-4-yl)-hydroxy-methyl]-5-isobutyl-imidazolidine-2,4-dione



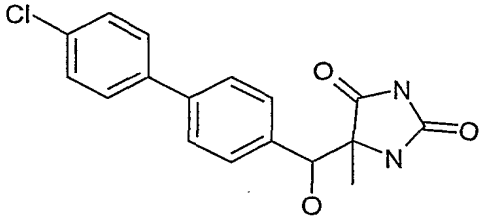
APCI-MS m/z: 357.1 [MH+].

5-[(4'-Chloro-biphenyl-4-yl)-hydroxy-methyl]-imidazolidine-2,4-dione



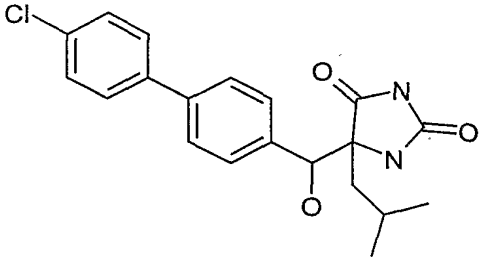
APCI-MS m/z: 298.9 [MH+ - H2O].

5-[(4'-Chloro-biphenyl-4-yl)-hydroxy-methyl]-5-methyl-imidazolidine-2,4-dione



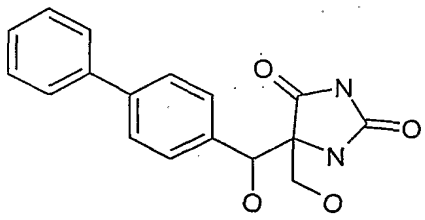
APCI-MS m/z: 331 [MH+].

5-[(4'-Chloro-biphenyl-4-yl)-hydroxy-methyl]-5-isobutyl-imidazolidine-2,4-dione



APCI-MS m/z: 373.1 [MH+].

5-(Biphenyl-4-yl)-hydroxy-methyl]-5-hydroxymethyl-imidazolidine-2,4-dione



APCI-MS m/z: 313.0 [MH+].

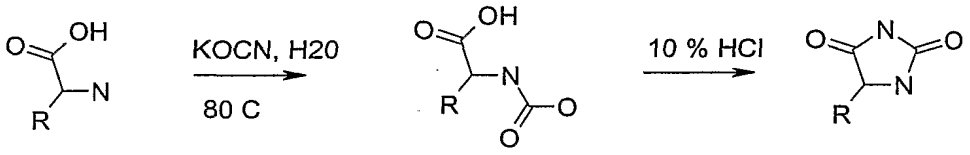
EXAMPLE 31

Compounds were synthesized according to Method C in Scheme 4 (shown in the description for compounds of formula III above).

(a) Preparation of intermediate hydantoins (Method A in Scheme 4)

According to Scheme 5 below, the hydantoins **5** were prepared in two steps from general amino acids **3** with isolation of the intermediates **4**.

Scheme 5 (Method A)



3 **4** **5**

Table 2 lists the intermediate hydantoins that were synthesized. The general method of preparation was as follows. A slurry of amino acid **3** (25 mmol) and potassium cyanate (5.1 g, 63 mmol) in water (75 ml) was heated at 80°C for approximately 1 hour. The clear solution was cooled to 0°C and acidified to approximately pH 1 with concentrated hydrochloric acid (aq). The resulting white precipitate **4** was heated at reflux for 0.5-1 hour and then cooled on ice. In some instances full conversion was not reached after 1 hour heating. In these cases the crude material was treated under the same protocol again. The white solid was filtered, washed with water, dried and analysed by HNMR and LCMS.

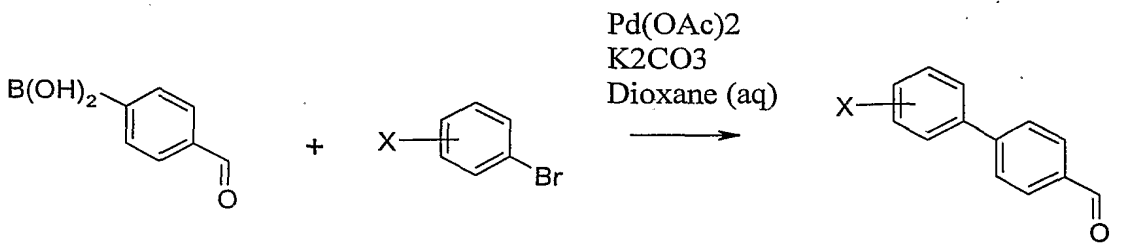
Table 2: intermediate hydantoins

Name:	Yield (%)	APCI-MS m/z: [MH^+]
5-(4-Chloro-benzyl)-imidazolidine-2,4-dione	87	224.9
[3-(2,5-Dioxo-imidazolidin-4-yl)-propyl]-carbamic acid benzyl ester	50	292.0
5-Isobutyl-imidazolidine-2,4-dione	85	157.0
5-Benzylsulfanylmethyl-imidazolidine-2,4-dione	87	237.0
5-Methylsulfanylmethyl-imidazolidine-2,4-dione	45	161.0
5-Cyclohexylmethyl-imidazolidine-2,4-dione	63	197.1
5-sec-Butyl-imidazolidine-2,4-dione	52	157.0
5-Phenethyl-imidazolidine-2,4-dione	94	205.1
5-Butyl-imidazolidine-2,4-dione	82	157.0
5-Isopropyl-imidazolidine-2,4-dione	49	
5-(1*H*5-Indol-3-ylmethyl)-imidazolidine-2,4-dione	94	230.0
5-(2-Hydroxy-ethyl)-imidazolidine-2,4-dione	36	

(b) Preparation of intermediate aldehydes (Method B in Scheme 4)

Substituted benzaldehydes where prepared by Suzuki coupling between different commercially available phenyl bromides and 4-formylphenylboronic acid, according to Scheme 6 below.

Scheme 6 (Method B)



4-pyridin-2-yl-benzaldehyde

The compound was prepared as follows. A mixture of 4-formylphenylboronic acid (195 mg,1.3 mmol), 2-bromopyridine (102.7 mg, 0.65mmol) and powdered K_2CO_3 (1.07g, 7.8 mmol) in dioxane (12 ml) and water (2 ml) was deoxygenated (vacuum and argon). Palladium diacetate (30 mg, 0.2 mol%) was added and the mixture was stirred for 2 hours at 80^0C under argon.

The slurry was cooled to room temperature. Filtration and evaporation afforded the crude product. Preparative HPLC (Chromasil C18 column, acetonitrile, water and trifluoroacetic acid), afforded the title compound 4-pyridin-2-yl-benzaldehyde (72 mg, in 60 % yield.

^{1}H NMR(400 MHz, DMSO-d6): δ 10.07 (1H, s); 8.73 (1H, d, J = 4.20Hz); 8.31 (2H, d, J = 8.20); 8.11 (1H, d, J = 8.01); 8.03 (2H, d, J = 8.20); 7.97 (1H, m).

APCI-MS m/z: 184.2 [MH+].

Other substituted benzaldehydes (listed in Table 3) were produced according to the same method.

Table 3: Substituted benzaldehydes

Name:	Yield (%)	APCI-MS m/z:
4'-Formyl-biphenyl-4-carbonitrile	65	208.0
4'-Formyl-biphenyl-3-carbonitrile		208.0
4'-Methoxy-biphenyl-4-carbaldehyde	50	213.1
3-Methoxy-biphenyl-4-carbaldehyde	62	213.1
Biphenyl-4,4'-dicarbaldehyde		211.0
Acetic acid 4'-formyl-biphenyl-3-yl ester		239.1
Acetic acid 4'-formyl-biphenyl-4yl ester		239.1
N-(4'-Formyl-biphenyl-3-yl)-acetamide	75	240.1
4'-Hydroxymethyl-biphenyl-4-carbaldehyde	55	213.1
3'-Fluoro-biphenyl-4-carbaldehyde	70	201.1

4-Pyridine-3-yl-benzaldehyde	67	184.2
3',4'-Difluoro-biphenyl-4-carbaldehyde	72	219.1
4-Pyridine-4-yl-benzaldehyde	67	184.2
N-[4-(4-Formyl-phenyl)-pyridine-2-yl]-acetamide	30	241.0
4-Benzo[1,3]dioxol-5-yl-benzaldehyde	20	226.1

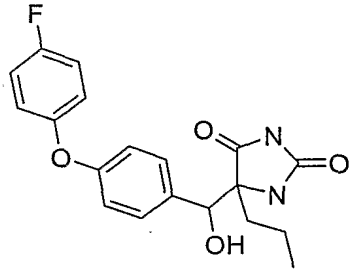
(c) Aldol condensation of intermediate hydantoins and aldehydes (Method C in Scheme 4)

The general procedure is exemplified by the synthesis of 5-{[4-(4-Fluoro-phenoxy)-phenyl]-methyl-methyl}-5-propyl-imidazolidine-2, 4-dione below.

5-{[4-(4-Fluoro-phenoxy)-phenyl]-methyl-methyl}-5-propyl-imidazolidine-2, 4-dione

Commercially available 4-(4-fluoro-phenoxy)-benzaldehyde (201.5 mg, 1.0 mmol), 5-propyl-hydantoin (438mg, 3.08 mmol) and 45 % aqueous trimethylamine (0.240 ml, 1.5 mmol) was refluxed in ethanol (12 ml) and water (3 ml) for 20 hours.

Evaporation and preparative HPLC(C18 column, acetonitrile, water and trifluoro acetic acid) afforded the title compound 5-{[4-(4-Fluoro-phenoxy)-phenyl]-methyl-methyl}-5-propyl-imidazolidine-2, 4-dione (11 mg, 0.03 mmol) in 3 % yield as white solid in form of the pure racemate.

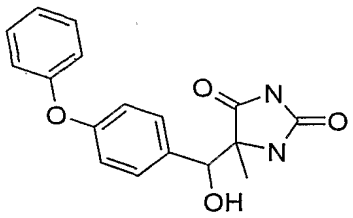


^{1}HNMR (300 MHz, DMSO-d_6): δ 10.71 (1H, s); 7.99 (1H, s); 7.70 (2H, dd, J = 4.38, 5.37 Hz); 7.75 (2H, d, J = 8.44 Hz); 7.35 (2H, d, J = 8.03 Hz); 7.27 (2H, dd, J = 4.59, 8.60 Hz); 5.89 (1H, d, J = 4.42 Hz); 4.66 (1H, d, J = 4.34 Hz); 1.96 (1H, dd, J = 12.89, 4.36 Hz); 1.71 (1H, dd; J = 12.95, 4.77 Hz); 1.32 (1H, m); 1.10 (1H, m); 0.89 (3H, t, J = 7.49 Hz).

APCI-MS m/z: 343.1 [MH^+ - OH].

The following compounds were produced according to the same method.

5-[4-phenoxy-phenyl]-hydroxy-methyl]-5-methyl-imidazolidine-2,4-dione

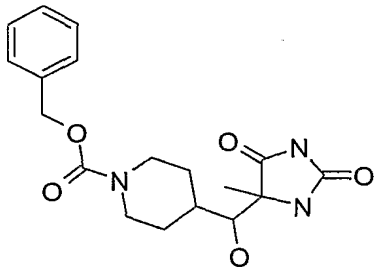


^{1}HNMR (400 MHz, DMSO-d_6): δ 10.12 (1H, bs); 8.06 (1H, s); 7.38 (2H, dd, J = 3.94, 7.60 Hz); 7.28 (2H, d, J = 8.62 Hz); 7.13 (1H, t, J =7.43 Hz); 6.96 (2H, d, J = 8.75 Hz); 6.91 (2H, d, J = 8.61 Hz); 5.89 (1H, d, J = 4.33 Hz); 4.62 (1H, d, J = 4.48 Hz); 1.41 (3H, s).

APCI-MS m/z: 313.0 [MH^+].

4-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidine-4-yl)-methyl]-piperidine-1-carboxylic acid benzyl ester.

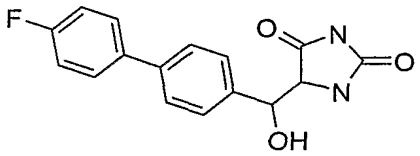
Prepared from commercially available starting materials.



APCI-MS m/z: 362.1[MH^+].

5-[(4'-Fluoro-biphenyl-4-yl)-hydroxy-methyl]-imidazolidine-2,4-dione

Prepared from commercially available starting materials.

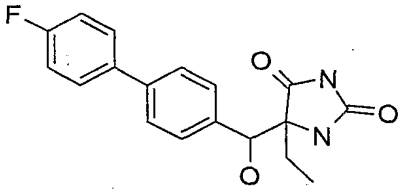


^{1}HNMR (400 MHz, DMSO-d_6): δ 10.32 (1H, s); 8.09 (1H, s); 7.71 (2H, dd, J = 4.47, 5.60 Hz); 7.60 (2H, d, J = 8.27 Hz); 7.38 (2H, d, J = 8.33 Hz); 7.28 (2H, dd, J = 5.05, 8.68 Hz); 5.88 (1H, d, J = 3.90 Hz); 4.97 (1H, t, J = 3.29 Hz); 4.39 (1H, d, J = 2.64 Hz).

APCI-MS m/z: 301.2 [MH^+].

5-Ethyl-5-[(4'-fluoro-biphenyl-4-yl)-hydroxy-methyl]-imidazolidine-2,4-dione

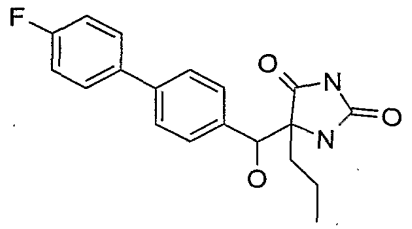
Produed by aldol condensation of 4'-fluoro-biphenyl-4-carbaldehyde and 5-Ethyl-imidazolide-2,4-dione.



1H NMR (400 MHz, DMSO-d6): δ 10.18 (1H, s); 7.96 (1H, s); 7.69 (2H, dd, J=8.77/5.53Hz); 7.57 (2H, d, J=8.20Hz); 7.35 (2H, d, J=8.20Hz); 7.26 (2H, t, J=8.87Hz); 5.87 (1H, d, J=4.39Hz); 4.66 (1H, d, 4.39Hz); 1.98 (1H, m); 1.75 (1H, m); 0.78 (3H, t, J=7.34Hz).

APCI-MS m/z: 329.1 [MH^+]

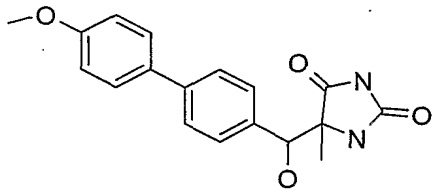
5-[(4'-fluoro-biphenyl-4-yl)-hydroxy-methyl]-5-propyl-imidazolidine-2,4-dione
Produced by aldol condensation of 4'-fluoro-biphenyl-4-carbaldehyde and 5-propyl-imidazolidine-2,4-dione.



1H NMR (400 MHz, DMSO-d6): δ 10.16 (1H, s); 7.98 (1H, s); 7.69 (2H, dd, J=8.68/5.44Hz); 7.56 (2H, d, J=8.20Hz); 7.34 (2H, d, J=8.20Hz); 7.26 (2H, t, J=8.77Hz); 5.87 (1H, d, J=4.39Hz); 4.64 (1H, d, 4.39Hz); 1.94 (1H, m); 1.70 (1H, m); 1.31 (1H, m); 1.10 (1H, m); 0.88 (3H, t, J=7.34Hz).

APCI-MS m/z: 343.1 [MH^+]

5-[Hydroxy-(4'-methoxy-biphenyl-4-yl)-methyl]-5-methyl-imidazolidine-2,4-dione
Produced by aldol condensation of 4'-Methoxy-biphenyl-4-carbaldehyde and 5-Methyl-imidazolidine-2,4-dione.

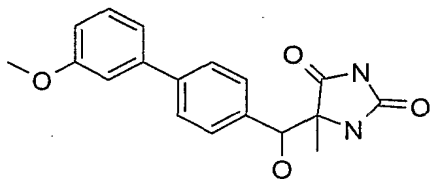


1H NMR (400 MHz, DMSO-d6): δ 10.16 (1H, s); 8.08 (1H, s); 7.59 (2H, d, J=8.77Hz); 7.52 (2H, d, J=8.20Hz); 7.31 (2H, d, J=8.20Hz); 6.99 (2H, d, J=8.58Hz); 5.87 (1H, d, J=4.39Hz); 4.63 (1H, d, 4.39Hz); 3.77 (3H, t); 1.42 (3H, s).

APCI-MS m/z: 327.1 [MH^+]

5-[Hydroxy-(3'-methoxy-biphenyl-4-yl)-methyl]-5-methyl-imidazolidine-2,4-dione

Produced by aldol condensation of 3-Methoxy-biphenyl-4-carbaldehyde and 5-Methyl-imidazolidine-2,4-dione.

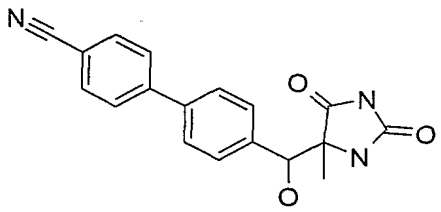


1H NMR (400 MHz, DMSO-d6): δ 10.18 (1H, s); 8.08 (1H, s); 7.59 (2H, d, J=8.01Hz); 7.35 (3H, m); 7.21 (1H, d, J=7.63Hz); 7.17 (1H, s); 6.91 (1H, dd, J=8.11/2.19); 5.91 (1H, d, J=4.39Hz); 4.65 (1H, d, 4.39Hz); 3.81 (3H, t); 1.43 (3H, s).

APCI-MS m/z: 327.1 [MH^+]

4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-carbonitrile

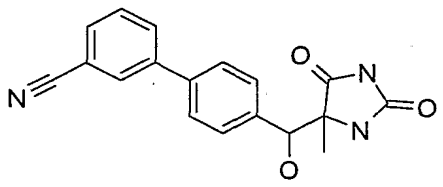
Produced by aldol condensation of 4'-Formyl-biphenyl-4-carbonitrile and 5-Methyl-imidazolidine-2,4-dione.



1H NMR (400 MHz, DMSO-d6): δ 10.18 (1H, s); 8.11 (1H, s); 7.89 (4H, m); 7.69 (2H, d, J=8.20); 7.40 (2H, d, J=8.20Hz); 5.97 (1H, d, J=4.39Hz); 4.67 (1H, d, 4.39Hz); 3.81 (3H, t); 1.43 (3H, s).

APCI-MS m/z: 322.1 [MH^+]

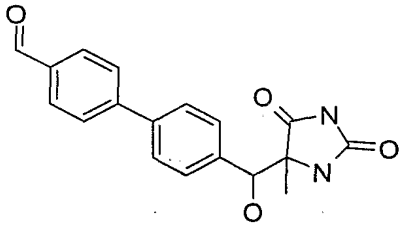
4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-3-carbonitrile
Produced by aldol condensation of 4'-Formyl-biphenyl-3-carbonitrile and 5-Methyl-imidazolidine-2,4-dione.



1H NMR (400 MHz, DMSO-d6): δ 10.18 (1H, s); 8.14 (1H, s); 8.11 (1H,s); 8.02 (1H, d, J=8.01Hz); 7.80 (1H, d, J=7.63Hz); 7.69 (2H, d, J=8.20Hz); 7.64 (1H, t, J=7.82Hz); 7.38 (2H, d, J=8.20Hz); 5.96 (1H, d, J=4.20Hz); 4.67 (1H, d, 3.81Hz); 1.42 (3H, s).

APCI-MS m/z: 322.1 [MH^+]

4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-carbaldehyde
Produced by aldol condensation of biphenyl-4-4'-dicarbaldehyde and 5-Methyl-imidazolidine-2,4-dione.

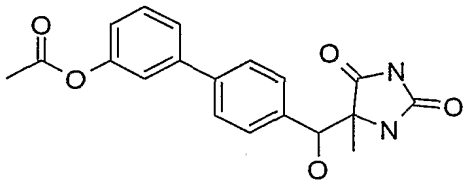


1H NMR (400 MHz, DMSO-d6): δ 10.19 (1H, s); 10.03 (1H, s); 8.12 (1H, s); 7.97 (2H, d, J=8.40Hz); 7.91 (2H, d, J=8.40); 7.71 (2H, d, J=8.20Hz); 7.40 (2H, d, J=8.40Hz); 5.97 (1H, d, J=4.39Hz); 4.67 (1H, d, 4.39Hz); 3.81 (3H, t); 1.43 (3H, s).

APCI-MS m/z: 325.1 [MH^+]

Acetic acid 4'-[hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-3-yl-ester

Produced by aldol condensation of acetic acid 4'-formyl-biphenyl-3-yl ester and 5-Methyl-imidazolidine-2,4-dione.

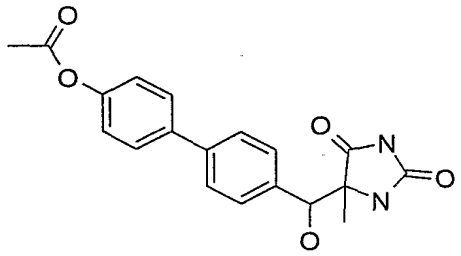


1H NMR (400 MHz, DMSO-d6): δ 10.18 (1H, s); 8.16 (1H, s); 8.11 (1H, s); 7.92 (1H, dd, J=7.72/1.24Hz); 7.66 (2H, d, J=8.40); 7.60 (1H, t, J=7.73Hz); 7.38 (2H, d, J=8.40Hz); 5.94 (1H, d, J=4.39Hz); 4.67 (1H, d, 4.39Hz); 2.63 (3H, s); 1.42 (3H, s).

APCI-MS m/z: 321.1 [MH^+-H_2O]

Acetic acid 4'-[hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-yl-ester

Produced by aldol condensation of acetic acid 4'-formyl-biphenyl-4yl ester and 5-Methyl-imidazolidine-2,4-dione.

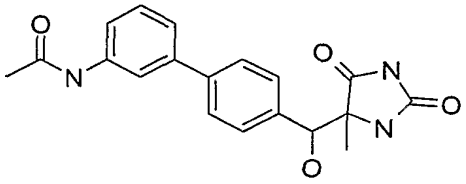


1H NMR (400 MHz, DMSO-d6): δ 10.19 (1H, s); 8.11 (1H, s); 8.01 (2H, d, J=8.39Hz); 7.82 (2H, d, J=8.20); 7.68 (2H, d, J=8.20Hz); 7.39 (2H, d, J=8.20Hz); 5.96 (1H, d, J=4.39Hz); 4.67 (1H, d, 4.39Hz); 2.59 (3H, t); 1.43 (3H, s).

APCI-MS m/z: 321.1 [MH^+-H_2O]

N-{4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-3-yl}-acetamide

Produced by aldol condensation of *N*-(4'-Formyl-biphenyl-3-yl)-acetamide and 5-Methyl-imidazolidine-2,4-dione.

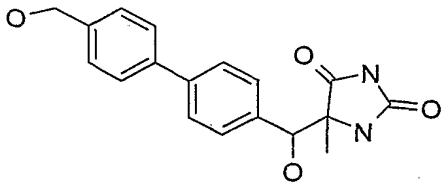


1H NMR (400 MHz, DMSO-d6): δ 10.17 (1H, s); 9.98 (1H, s); 8.08 (1H, s); 7.87 (1H, s); 7.50 (3H, m); 7.32 (4H, m); 5.91 (1H, d, J=4.56Hz); 4.64 (1H, d, 4.28Hz); 2.05 (3H, s); 1.42 (3H, s).

APCI-MS m/z: 354.1 [MH^+]

5-[Hydroxy-(4-hydroxymethyl-biphenyl-4-yl)-methyl]-5-methyl-imidazolidine-2,4-dione

Produced by aldol condensation of 4'-Hydroxymethyl-biphenyl-4-carbaldehyde and 5-Methyl-imidazolidine-2,4-dione.

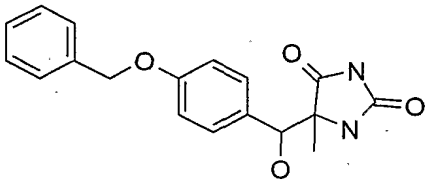


1H NMR (400 MHz, DMSO-d6): δ 10.17 (1H, s); 8.09 (1H, s); 7.61 (2H, d, J=8.20Hz); 7.57 (2H, d, J=8.20); 7.38 (2H, d, J=8.20Hz); 7.34 (2H, d, J=8.20Hz); 5.90 (1H, d, J=4.39Hz); 5.19 (1H, T, J=5.72Hz); 4.65 (1H, d, 4.39Hz); 4.52 (2H, d, J=5.72Hz); 1.43 (3H, s).

APCI-MS m/z: 327.1 [MH^+]

5-[(4-Benzyloxy-phenyl)-hydroxy-methyl]-5-methyl-imidazolidine-2,4-dione

Produced by aldol condensation of 4-benzyloxy-benzaldehyde and 5-Methyl-imidazolidine-2,4-dione.

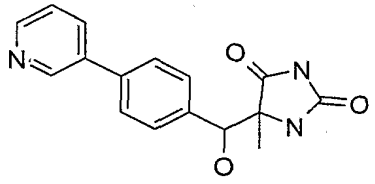


1H NMR (400 MHz, DMSO-d6): δ 10.10 (1H, s); 8.01 (1H, s); 7.46-7.27 (5H, m); 7.18 (2H, d, J=8.58Hz); 6.89 (2H, d, J=8.58Hz); 5.75 (1H, d, J=4.39Hz); 5.04 (2H, s); 4.55 (1H, d, J=4.39Hz); 1.43 (3H, s).

APCI-MS m/z: 309.1 [MH^+-H_2O]

5-[Hydroxy-(4pyridine-3-yl-phenyl)-methyl]-5-methyl-imidazolidine-2,4-dione

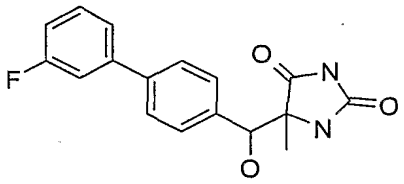
Produced by aldol condensation of 4-Pyridine-3-yl-benzaldehyde and 5-Methyl-imidazolidine-2,4-dione.



APCI-MS m/z: 298.1 [MH^+]

5-[(3'-Fluoro-biphenyl-4-yl)-hydroxy-methyl]-5-methyl-imidazolidine-2,4-dione

Produced by aldol condensation of 3'-Fluoro-biphenyl-4-carbaldehyde and 5-Methyl-imidazolidine-2,4-dione.

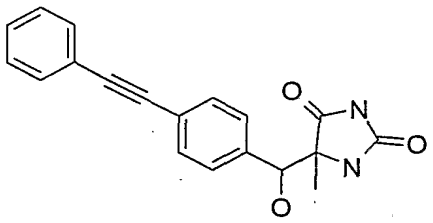


1H NMR (400 MHz, DMSO-d6): δ 10.17 (1H, s); 8.10 (1H, s); 7.63 (1H, d, J=8.20Hz); 7.49 (3H, m); 7.36 (2H, d, J=8.20Hz); 7.17 (1H, m); 5.93 (1H, d, J=4.20Hz); 4.66 (1H, d, 3.81Hz); 1.42 (3H, s).

APCI-MS m/z: 315 [MH^+]

5-[Hydroxy-(4-phenylethenyl-phenyl)-methyl]-5-methyl-imidazolidine-2,4-dione

The starting aldehyde was synthesized according; Thorand S. *et.al* (J Org Chem 1998, 63(23), 8551-8553).

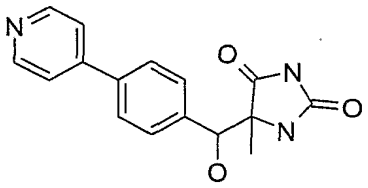


1H NMR (400 MHz, DMSO-d6): δ 10.18 (1H, s); 8.08 (1H, s); 7.53 (2H, m); 7.45 (2H, d, J=8.40Hz); 7.41 (3H, m); 7.30 (2H, d, J=8.20Hz); 5.99 (1H, d, J=4.58Hz); 4.64 (1H, d, 4.39Hz); 1.41 (3H, s).

APCI-MS m/z: 321.1 [MH^+]

5-[Hydroxy-(4pyridine-4-yl-phenyl)-methyl]-5-methyl-imidazolidine-2,4-dione

Produced by aldol condensation of 4-Pyridine-4-yl-benzaldehyde and 5-Methyl-imidazolidine-2,4-dione.

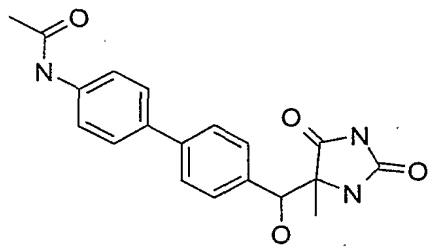


1H NMR (400 MHz, DMSO-d6): δ 10.19 (1H, s); 8.61 (2H, m); 8.12 (1H, s); 7.74 (2H, d, J=8.39); 7.70 (2H, m); 7.41 (2H, d, J=8.20Hz); 5.99 (1H, s,); 4.67 (1H, s); 1.42 (3H, s).

APCI-MS m/z: 298.1 [MH^+]

***N*-{4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-yl}-acetamide**

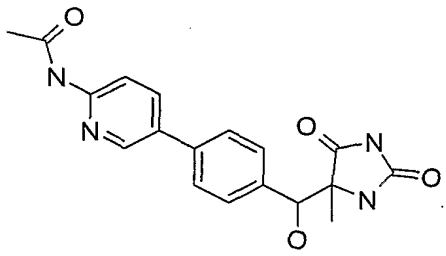
Produced by aldol condensation of N-(4'-formyl-biphenyl-4-yl)-acetamide and 5-Methyl-imidazolidine-2,4-dione.



APCI-MS m/z: 354.1 [MH^+]

N-(5-{4-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-phenyl}-pyridin-2-yl)-acetamide

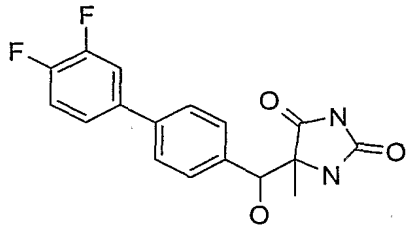
Produced by aldol condensation of *N*-[4-(4-Formyl-phenyl)-pyridine-2-yl]-acetamide and 5-Methyl-imidazolidine-2,4-dione.



APCI-MS m/z: 355.1 [MH^+]

5-[(3',4'-Difluoro-biphenyl-4-yl)-hydroxy-methyl]-5-methyl-imidazolidine-2,4-dione

Produced by aldol condensation of 3',4'-Difluoro-biphenyl-4-carbaldehyde and 5-Methyl-imidazolidine-2,4-dione.

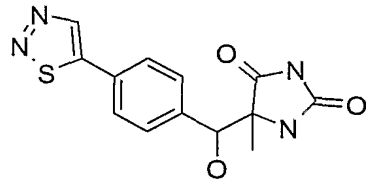


1H NMR (400 MHz, DMSO-d6): δ 10.16 (1H, s); 8.10 (1H, s); 7.75 (1H, m); 7.61 (2H, d, J=8.27Hz); 7.50 (2H, m); 7.35 (2H, d, J=8.27); 5.93 (1H, d, J=3.99Hz); 4.66 (1H, d, 3.98Hz); 1.41 (3H, s).

APCI-MS m/z: 333 [MH^+]

5-[Hydroxy-(4-[1,2,3]thiadiazol-5-yl-phenyl)-methyl]-5-methyl-imidazolidine-2,4-dione

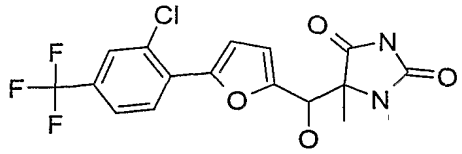
Produced by aldol condensation of 4-[1,2,3]Thiadiazol-5-yl-benzaldehyde and 5-Methyl-imidazolidine-2,4-dione.



APCI-MS m/z: 305 [MH^+]

5-{[5-(2-Chloro-4-trifluoromethyl-phenyl)-furan-2-yl]-hydroxy-methyl}-5-methyl-imidazolidine-2,4-dione

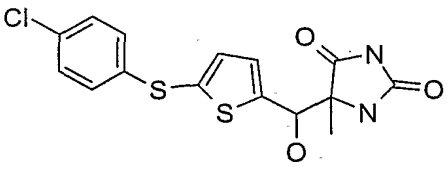
Produced by aldol condensation of 5-(3-chloro-4-trifluoromethyl-phenyl)-furan-2-carbaldehyde and 5-Methyl-imidazolidine-2,4-dione.



APCI-MS m/z: 389 [MH^+]

5-{[5-(4-Chloro-phenylsulfanyl)-thiophen-2-yl]-hydroxy-methyl}-5-methyl-imidazolidine-2,4-dione

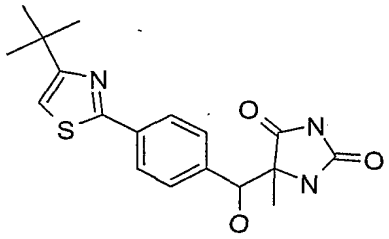
Produced by aldol condensation of 5-(4-chloro-phenylsulfanyl)-thiophene-2-carbaldehyde and 5-Methyl-imidazolidine-2,4-dione.



APCI-MS m/z: 350.9 [$MH^+ - H_2O$]

5-{[4-(4-*tert*-Butyl-thiazol-2-yl)-phenyl]-hydroxy-methyl}-5-methyl-imidazolidine-2,4-dione

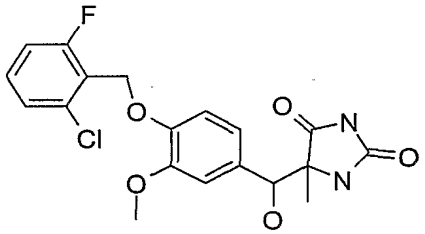
Produced by aldol condensation of 4-(4-tert-butyl-thiazol-2-yl)-benzaldehyde and 5-Methyl-imidazolidine-2,4-dione.



APCI-MS m/z: 360 [MH^+]

5-{[4-(2-Chloro-6-fluoro-benzyloxy)-3-methoxy-phenyl]-hydroxy-methyl}-5-methyl-imidazolidine-2,4-dione

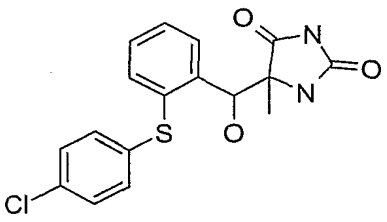
Produced by aldol condensation of 4-(2-chloro-6-fluoro-benzyloxy)-3-methoxy-bemnzaldehyde and 5-Methyl-imidazolidine-2,4-dione.



APCI-MS m/z: 391 [MH^+-H_2O]

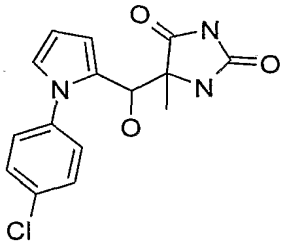
5-{[2-(4-Chloro-phenylsulfanyl)-phenyl]-hydroxy-methyl}-5-methyl-imidazolidine-2,4-dione

Produced by aldol condensation of 2-(4-chloro-phenylsulfanyl)-benzaldehyde and 5-Methyl-imidazolidine-2,4-dione.



5-{[1-(4-Chloro-phenyl*H*-pyrrol-2-yl]-hydroxy-methyl}-5-methyl-imidazolidine-2,4-dione

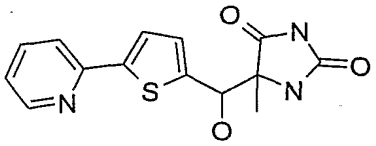
Produced by aldol condensation of 1-(4-Chloro-phenyl-1*H*-pyrrol-2-carbaldehyde and 5-Methyl-imidazolidine-2,4-dione.



APCI-MS m/z: 302.1 [MH^+ -H_2O]

5-[Hydroxy-(2-pyridin-2-yl-thiophen-2-yl)-methyl]-5-methyl-imidazolidine-2,4-dione

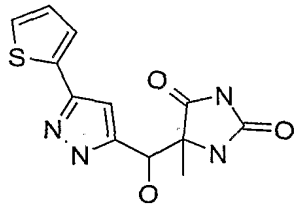
Produced by aldol condensation of 5-pyridin-2-yl-thiophen-2-carbaldehyde and 5-Methyl-imidazolidine-2,4-dione.



APCI-MS m/z: 304 [MH^+]

5-[Hydroxy-(5-thiophen-2-*H*-pyrazol-3-yl)-methyl]-5-methyl-imidazolidine-2,4-dione

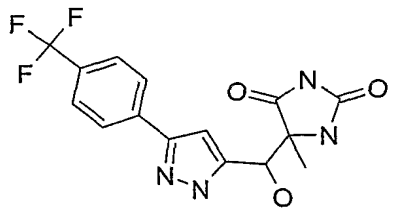
Produced by aldol condensation of 5-thiophen-2-yl-2*H*-pyrazol-3-carbaldehyde and 5-Methyl-imidazolidine-2,4-dione.



APCI-MS m/z: 293.1 [MH^+]

5-{Hydroxy-[5-(4-trifluoromethyl-phenyl *H*-pyrazol-3-yl]-5-methyl-imidazolidine-2,4-dione

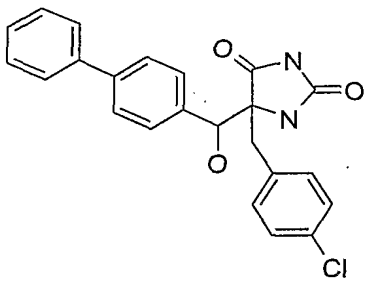
Produced by aldol condensation of 5-(4-trifluoromethyl-phenyl-2*H*-pyrazol-3-carbaldehyde and 5-Methyl-imidazolidine-2,4-dione.



APCI-MS m/z: 355 [MH^+]

5-(Biphenyl-4-yl-hydroxy-methyl)-5-(4-chloro-benzyl)-imidazolidine-2,4-dione

Produced by aldol condensation of biphenyl-4-carbaldehyde and 5-(4-chloro-benzyl)-imidazolidine-2,4-dione.



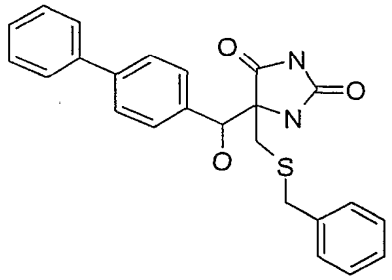
1H NMR (400 MHz, DMSO-d6): δ 9.89 (1H, s); 8.29 (1H, s); 7.65 (2H, d, J=7.73Hz); 7.59 (2H, d, J=8.20Hz); 7.43 (2H, m); 7.39 (2H, d, J=8.20Hz); 7.32 (3H, m); 7.20 (2H, d,

J=8.39Hz); 6.13 (1H, d, J=4.01Hz); 4.85 (1H, d, 4.01Hz); 3.28 (1H, d, J=13.35Hz); 3.04 (1H, d, J=13.35).

APCI-MS m/z: 407.2 [MH^+]

5-Benzylsulfanylmethyl-5-(biphenyl-4-yl-hydroxy-methyl)-imidazolidine-2,4-dione

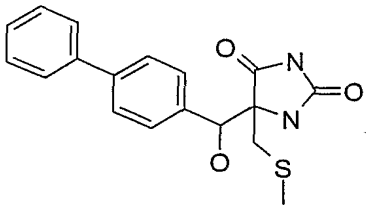
Produced by aldol condensation of biphenyl-4-carbaldehyde and 5-Benzylsulfanylmethyl-imidazolidine-2,4-dione.



APCI-MS m/z: 419.2 [MH^+]

5-(Biphenyl-4-yl-hydroxy-methyl)-5-methylsulfanylmethyl-imidazolidine-2,4-dione

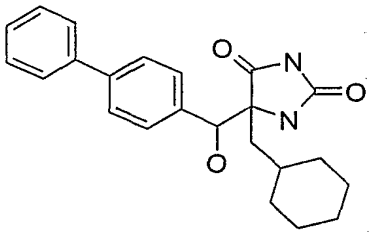
Produced by aldol condensation of biphenyl-4-carbaldehyde and 5-methylsulfanylmethyl-imidazolidine-2,4-dione.



APCI-MS m/z: 343.1 [MH^+]

5-(Biphenyl-4-yl-hydroxy-methyl)-5-cyclohexylmethyl-imidazolidine-2,4-dione

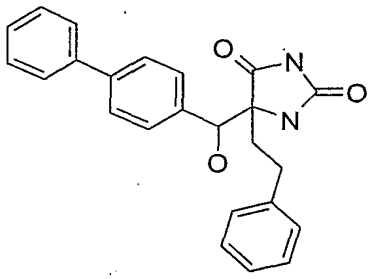
Produced by aldol condensation of biphenyl-4-carbaldehyde and 5-cyclohexylmethyl-imidazolidine-2,4-dione.



APCI-MS m/z: 379.3 [MH^+]

5-(Biphenyl-4-yl-hydroxy-methyl)-5-phenylethyl-imidazolidine-2,4-dione

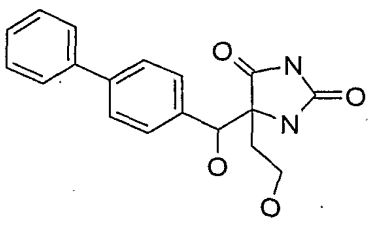
Produced by aldol condensation of biphenyl-4-carbaldehyde and 5-phenylethyl-imidazolidine-2,4-dione.



APCI-MS m/z: 387.3 [MH^+]

5-(Biphenyl-4-yl-hydroxy-methyl)-5-(2-hydroxy-ethyl)-imidazolidine-2,4-dione

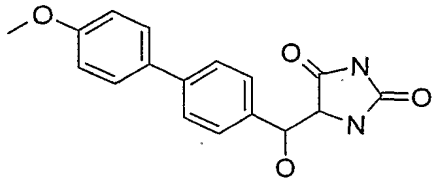
Produced by aldol condensation of biphenyl-4-carbaldehyde and 5-(2-hydroxy-ethyl)-imidazolidine-2,4-dione.



APCI-MS m/z: 309.2 [$MH^+ - H_2O$]

5-[Hydroxy-(4'-methoxy-biphenyl-4-yl)-methyl]-imidazolidine-2,4-dione

Produced by aldol condensation of 4'-methoxy-biphenyl-4-carbaldehyde and imidazolidine-2,4-dione.

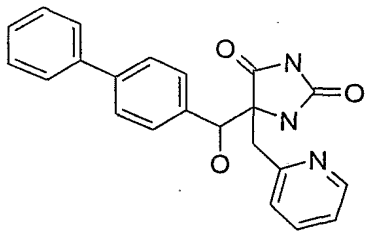


1H NMR (400 MHz, DMSO-d6): δ 10.30 (1H, s); 8.06 (1H, s); 7.60 (2H, d, J=8.77Hz); 7.54 (2H, d, J=8.39Hz); 7.33 (2H, d, J=8.20Hz); 7.00 (2H, d, J=8.77Hz); 5.83 (1H, d, J=3.81Hz); 4.94 (1H, t, J=3.34); 4.33 (1H, d, J=2.67Hz); 3.77 (3H, s).

APCI-MS m/z: 295 [MH^+-H_2O]

5-(Biphenyl-4-yl-hydroxy-methyl)-5-pyridin-4-ylmethyl-imidazolidine-2,4-dione

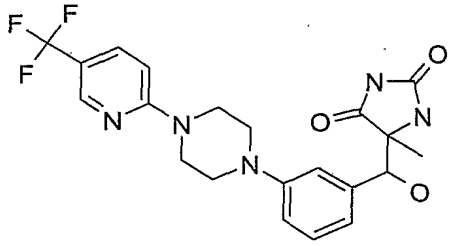
Produced by aldol condensation of biphenyl-4-carbaldehyde and 5-pyridin-4-ylmethyl-imidazolidine-2,4-dione.



APCI-MS m/z: 374.2 [MH^+]

5-(Hydroxy-{3-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-phenyl}methyl)-5-methyl-imidazolidine-2,4-dione

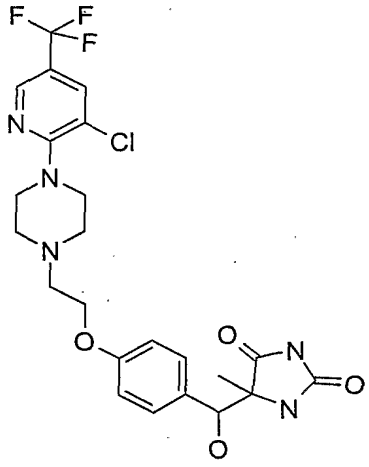
Produced by aldol condensation of4-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-benzaldehyde and 5-Methyl-imidazolidine-2,4-dione.



APCI-MS m/z: 450.2 [MH^+]

5-[(4-{2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethoxy}-phenyl)-hydroxy-methyl]]-5-methyl-imidazolidine-2,4-dione

Prepared from commercially available starting materials.



APCI-MS m/z: 528.3 [MH^+].

EXAMPLE 32

Compounds were synthesized according to Method D (Suzuki coupling) in Scheme 4 (shown in the description above) from commercially available arylboronic acids and 5-[Hydroxy-(4-iodo-phenyl)-methyl]-5-methyl-imidazolidine-2,4-dione or 5-[Hydroxy-(4-iodo-phenyl)-methyl]-imidazolidine-2,4-dione described below.

5-[Hydroxy-(4-iodo-phenyl)-methyl]-5-methyl-imidazolidine-2,4-dione

4-Iodo-bensaldehyde (9.280 g, 40.0 mmol), 5-methyl-hydantoin (4.564 g, 40.0 mmol) and 45 % aques trimethylamine (6.40 ml, 40.0 mmol) was refluxed in ethanol (60 ml) and water (40 ml) for 20 hours under an atmosphere of nitrogen. A white precipitate was formed. After cooling at room temperature for approximately 15 minutes the precipitate was collected by filtration, washed sequentially with ethanol (50%, 50 ml), water (50 ml) and diethyl ether (50 ml). Drying by air suction afforded the title compound 5-[hydroxyl-(4-iodo-phenyl)-methyl]-imidazolidine-2, 4-dione (7.968 g, 23.0 mol) in 57.5 % yield as white solid in form of the pure racemate.

^{1}HNMR (300 MHz, DMSO-d_6): δ 10.19 (1H, s); 8.08 (1H, s); 7.64 (2H, d, J = 8.55Hz); 7.07 (2H, d, J = 8.43 Hz); 5.98 (1H, d, J = 4.49 Hz); 4.57 (1H, d, J = 4.32 Hz); 1.40 (3H, s).

APCI-MS m/z: 346.9 [MH^+].

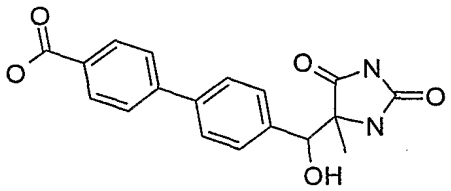
5-[Hydroxy-(4-iodo-phenyl)-methyl]-imidazolidine-2,4-dione

Prepared according to the same protocol used for preparation of 5-[Hydroxy-(4-iodo-phenyl)-methyl]-5-methyl-imidazolidine-2,4-dione described above.

^{1}HNMR (300 MHz, DMSO-d_6): δ 10.32 (1H, s); 8.06 (1H, s); 7.66 (2H, d, J = 8.14 Hz); 7.10 (2H, d, J = 8.27 Hz); 5.91 (1H, d, J = 3.90 Hz); 4.87 (1H, t, J = 2.70 Hz); 4.34 (1H, d, J = 2.48 Hz).

APCI-MS m/z: 333.1 [MH^+].

4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-carboxylic acid



A stirred mixture of 4-Carboxy-phenyl-boronic acid (214 mg, 1.3 mmol), 5-[hydroxy-(4-iodo-phenyl)-methyl]-imidazolidine-2,4-dione (347 mg, 1.0 mmol) and sodium hydrogencarbonate (318 mg, 3.8 mmol) in acetone (5.0 ml) and water (5.0 ml) was deoxygenated by vacuum/nitrogene exchange 3 times. Palladium diacetate (20 mg, yyy mmol) was added and deoxygenating repeated, and then the mixture was stirred at 50°C for 90 min under an atmosphere of nitrogen.

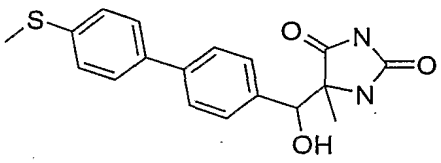
The solid was allowed to precipitate. The supernatant was partitioned between water (20 ml), ethyl acetate (15 ml) and diethyl ether (15 ml). The water phase was acidified with 1 M HCl (aq, 10 ml) then extracted two times with ethyl acetate (15 ml) and diethyl ether (15 ml). Evaporation of the organic phase afforded 340 mg of the crude product, this was slurred in dioxane (6 ml) and water (6 ml) together with trifluoroacetic acid (100 microl) and filtrated. Preparative HPLC (column, acetonitril/water/trifluoro acetic acid) afforded the title compound 4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-carboxylic acid (114 mg, 0.33 mmol) as a white solid in 33.5 % yield.

^{1}HNMR (400 MHz, DMSO-d_6): δ 10.20 (1H, s); 8.13 (1H,s); 8.00 (2H, d, J = 8.33 Hz); 7.79 (2H, d, J = 8.49 Hz); 7.67 (2H, d, J = 8.39 Hz); 7.40 (2H, d, J = 8.48 Hz); 5.97 (1H, bs); 4.68 (1H, s); 1.44 (3H, s).

APCI-MS m/z: 341 [MH^+].

The following compounds where prepared by the same protocol used for preparation of 4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-carboxylic acid described above.

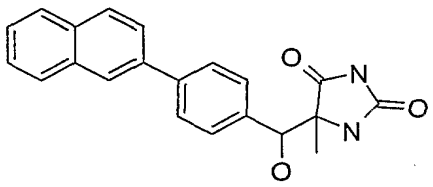
5-[Hydroxy-(4'-methylsulfanyl-biphenyl-4-yl)-methyl]-5-methyl-imidazolidine-2,4-dione



^{1}HNMR (300 MHz, DMSO-d_6): δ 10.18 (1H, s); 8.10 (1H, s); 7.62 (2H, d, J = 8.61 Hz); 7.57 (2H, d, J = 8.42 Hz); 7.35 (2H, d, J = 5.73 Hz); 7.32 (2H, d, J = 6.30 Hz); 5.91 (1H, d, J = 4.32 Hz); 4.65 (1H, d, J = 4.31 Hz); 2.50 (3H, s); 1.43 (3H, s).

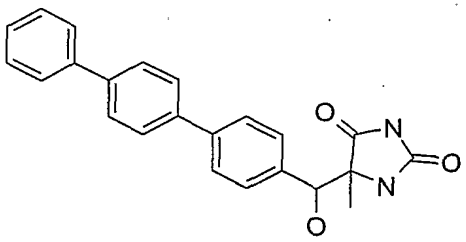
APCI-MS m/z: 343.0 [MH^+].

5-[Hydroxy-(4-naphtalen-2-yl phenyl)-methyl]-5-methyl-imidazolidine-2,4-dione



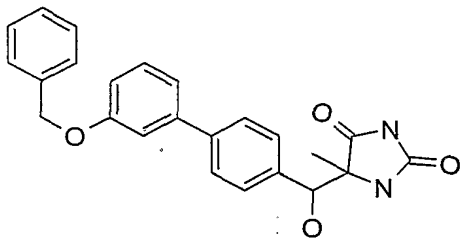
APCI-MS m/z: 347.1 [MH^+]

5-[Hydroxy-[1,1';4,1'']terpenyl-4''-yl –methyl)-5-methyl-imidazolidine-2,4-dione



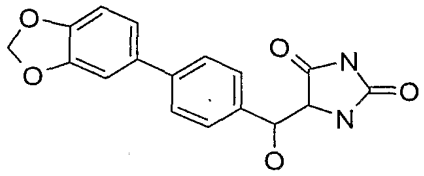
APCI-MS m/z: 373.1 [MH^+]

5-[(3'-Benzyloxy-biphenyl-4-yl)-hydroxy-methyl]-5-methyl-imidazolidine-2,4-dione



APCI-MS m/z: 403.1 [MH^+].

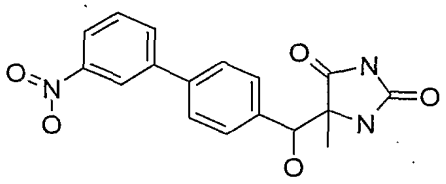
5-[(4-Benzo[1,3]dioxol-5-yl-phenyl)-hydroxy-methyl]-imidazolidine-2,4-dione



1H NMR (400 MHz, DMSO-d6): δ 10.31 (1H, s); 8.04 (1H, s); 7.53 (2H, d, J=8.39Hz); 7.33 (2H, d, J=8.20Hz); 7.24 (1H, s); 7.14 (1H, d, J=8.11Hz); 6.97 (1H, d, J=8.01Hz); 6.03 (2H, d, J=6.87Hz); 5.84 (1H, d, J=3.62Hz); 4.92 (1H, s); 4.35 (1H, s).

APCI-MS m/z: 309 [$MH^+ - H_2O$]

5-[Hydroxy-(3'-nitro-biphenyl-4-yl)-methyl]-5-methyl-imidazolidine-2,4-dione

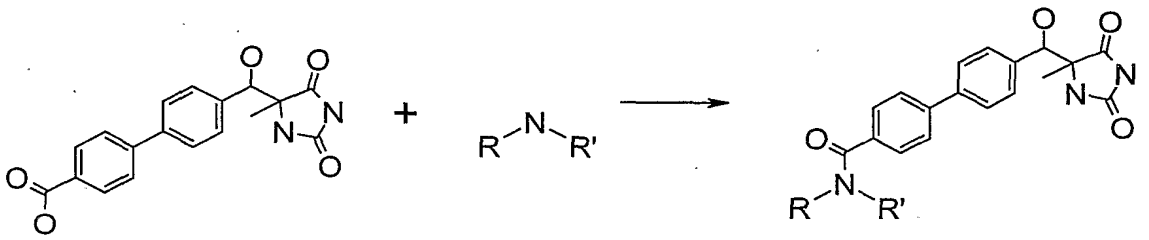


1H NMR (400 MHz, DMSO-d6): δ 10.18 (1H, s); 8.41 (1H, t, J=8.41Hz); 8.20 (1H, m); 8.15 (1H, m); 8.12 (1H, s); 7.73 (3H, m); 7.41 (2H, d, J=8.20); 5.97 (1H, d, J=4.39Hz); 4.68 (1H, d, 4.58Hz); 1.43 (3H, s).

APCI-MS m/z: 342.1 [MH^+]

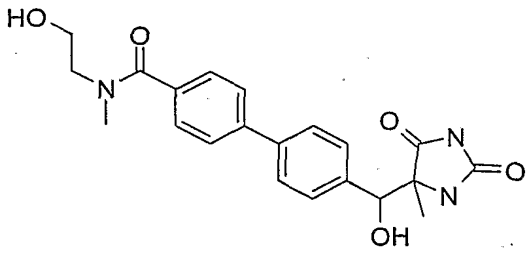
EXAMPLE 33

Compounds were synthesized according to Method E (Amide coupling) in Scheme 4 (shown in the description above). The compounds were prepared by the general method described below. All amines used in the coupling are commercially available.



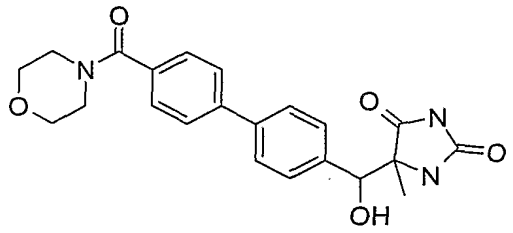
To a 0.3M solution of 4'-[hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-carboxylic acid in 1-methyl-2-pyrrolidinone (50μL) was 1-ethyl-3(3-dimethylaminopropyl)carbdiimide hydrochloride (1.3eq ,45μL 0.5M in 1-methyl-2-pyrrolidinone) , 1-hydroxybenzotriazole (1.7eq, 51μL 0.5M in 1-methyl-2-pyrrolidinone), N,N-disipropylethylamine (1eq , 20μL 1M in 1-methyl-2-pyrrolidinone) and the corresponding amine (2eq , 100μL 0.3M in 1-methyl-2-pyrrolidinone) added. The reaction mixture was stirred over night at room temperature. Purification was made by preparative HPLC-C_{18}.

4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-carboxylic acid (2-hydroxy-ethyl)-methyl-amide



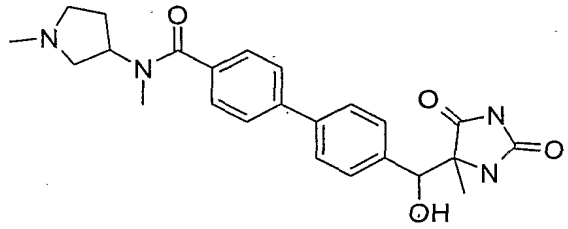
APCI-MS m/z: 398.1 [MH^+]

5-{Hydroxy-[4'-(morpholine-4-carbonyl)-biphenyl-4-yl]-methyl}-5-methyl-imidazolidine-2,4-dione



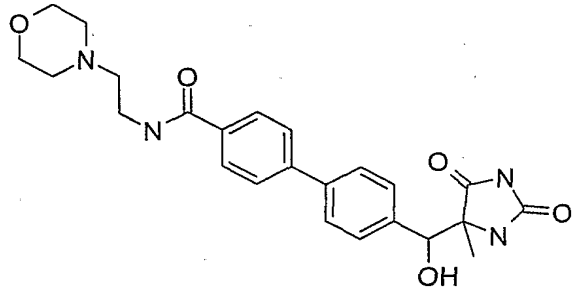
APCI-MS m/z: 410.1 [MH^+]

4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-carboxylic acid methyl-(1-methyl-pyrrolidin-3-yl)-amide



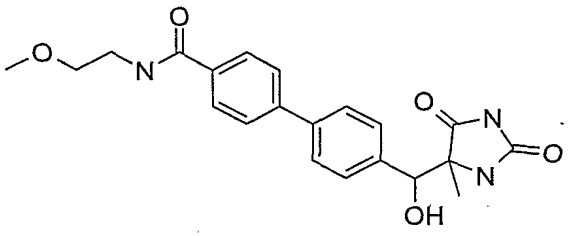
APCI-MS m/z: 437.1 [MH^+]

4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-carboxylic acid (2-morpholin-4-yl-ethyl)-amide



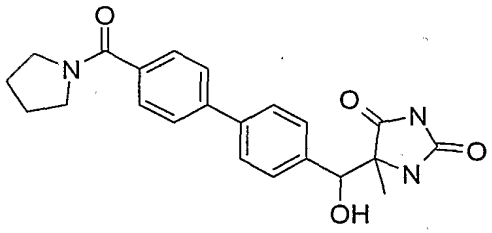
APCI-MS m/z: 453.1 [MH^+]

4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-carboxylic acid (2-methoxy-ethyl)-amide



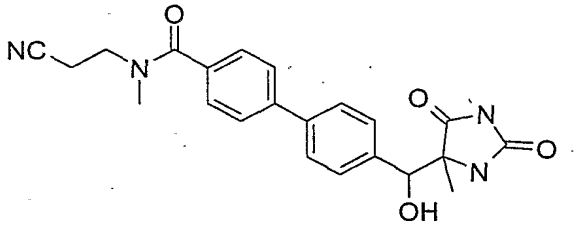
APCI-MS m/z: 398.1 [MH^+]

5-{Hydroxy-[4'-(pyrrolidine-1-carbonyl)-biphenyl-4-yl]-methyl}-5-methyl-imidazolidine-2,4-dione



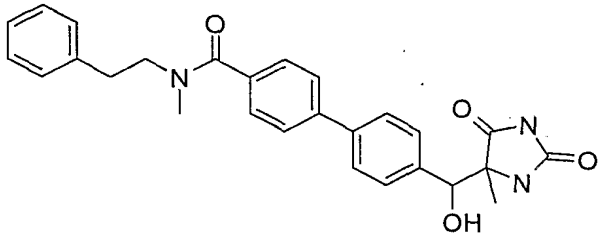
APCI-MS m/z: 394.1 [MH^+]

4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-carboxylic acid (2-cyano-ethyl)-methyl-amide



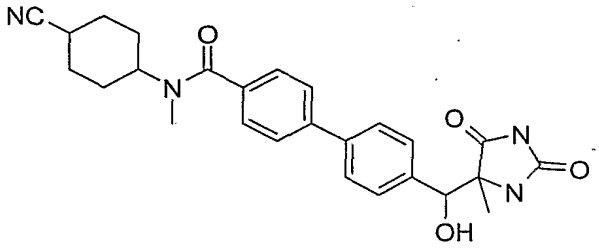
APCI-MS m/z: 407.1 [MH^+]

4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-carboxylic acid methyl-phenethyl-amide



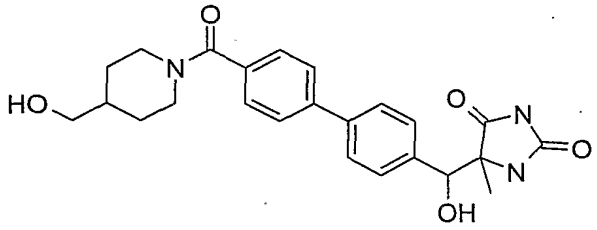
APCI-MS m/z: 458.1 [MH^+]

4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-carboxylic acid (4-cyano-cyclohexyl)-methyl-amide



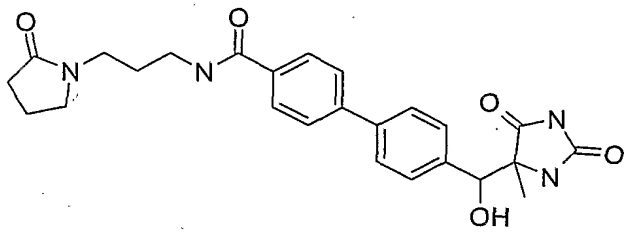
APCI-MS m/z: 461.1 [MH^+]

5-{Hydroxy-[4'-(4-hydroxymethyl-piperidine-1-carbonyl)-biphenyl-4-yl]-methyl}-5-methyl-imidazolidine-2,4-dione



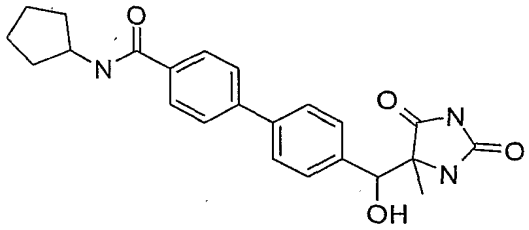
APCI-MS m/z: 438.1 [MH^+]

4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-carboxylic acid [3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide



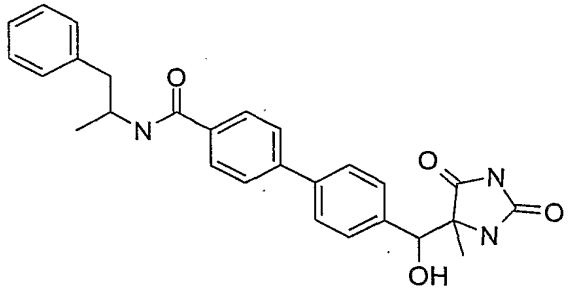
APCI-MS m/z: 465.1 [MH^+]

4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-carboxylic acid cyclopentylamide



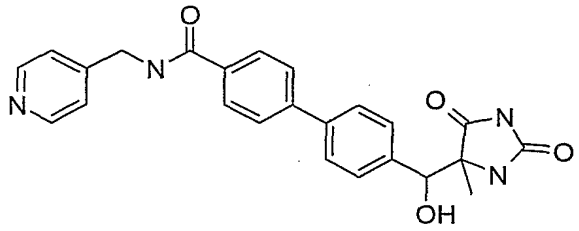
APCI-MS m/z: 408.1 [MH^+]

4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-carboxylic acid (1-phenyl-ethyl)-amide



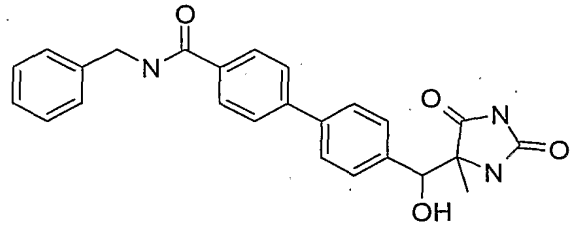
APCI-MS m/z: 444.1 [MH^+]

4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-carboxylic acid (pyridin-4-ylmethyl)-amide



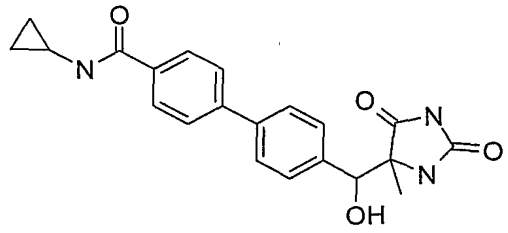
APCI-MS m/z: 431.1 [MH^+]

4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-carboxylic acid benzylamide



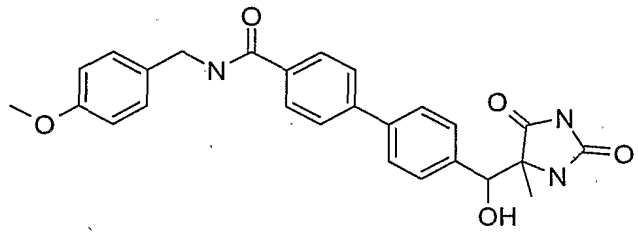
APCI-MS m/z: 430.1 [MH^+]

4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-carboxylic acid cyclopropylamide



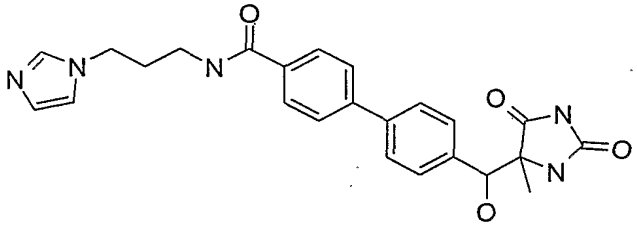
APCI-MS m/380.1 [MH^+]

4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-carboxylic acid 4-methoxy-benzylamide



APCI-MS m/z: 460.1 [MH^+]

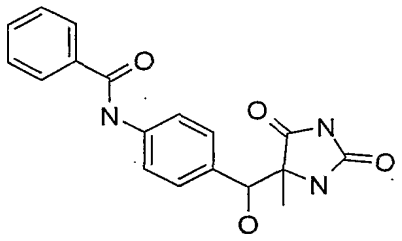
4'-[Hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-biphenyl-4-carboxylic acid (3-imidazol-1-yl-propyl)-amide



APCI-MS m/z: 448.1 [MH^+]

***N*-{4-[Hydroxy-(4-methyl-2,5-dioxo-imidazolodin-4-yl)-methyl]-phenyl}-benzamide**

5-[Hydroxy-(4-nitro-phenyl)-methyl]-5-methyl-imidazolidine-2,4-dione was synthesized according to method C by the protocol described in Example 24 (APCI-MS m/z: 268.8 [MH^+]). The corresponding amine 5-[(4-Amino-phenyl)-hydroxy-methyl]-5-methyl-imidazolidine-2,4-dione was afforded by Pd(0) catalysed hydrogenation in Ethanol (APCI-MS m/z: 218.0 [MH^+] (-H20)). 5-[(4-Amino-phenyl)-hydroxy-methyl]-5-methyl-imidazolidine-2,4-dione was finaly coupled with benzoic acid according to the protocol above (Method E) to afford the title compound.

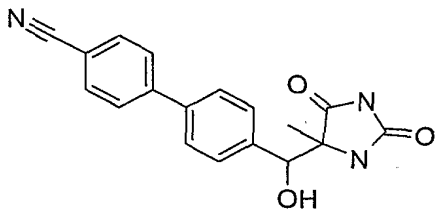


APCI-MS m/z: 240.0 [MH^+]

EXAMPLE 34

Enantiomeres where isolated by the method described for the resolution of 4'-(hydroxy-(4-methyl-2,5-dioxoimidazolidin-4-yl)-methyl)biphenyl-4-carbonitrile below.

4'-(hydroxy-(4-methyl-2,5-dioxoimidazolidin-4-yl)-methyl)biphenyl-4-carbonitrile



Chromatographic resolution:

0.10 g of diastereomerically pure 4'-(hydroxy-(4-methyl-2,5-dioxoimidazolidin-4-yl)-methyl)biphenyl-4-carbonitrile was dissolved in 76 mL absolute ethanol/ *iso*-hexane (75:25) and filtered through a 0.45 μm nylon filter. Volumes of 5.0 mL were injected repeatedly on a chiral column (Chiralpak AD-H (2 cm ID x 25 cm L)) connected to a UV-detector (254 nm) and fraction collector. Separation was performed with absolute ethanol/ *is*-hexane (75:25) at 8.0 mol /min flow and the pure enantiomers eluted after approximately 15 and 21 minutes, respectively. Fractions containing the same enantiomer were combined, concentrated and assessed for optical purity by chiral chromatography (see below).

Enantiomer A ("early" fractions)

Yield: 0.047 g white solid

Chiral chromatography (Chiralpak AD-H (0.45 cm I.D x 25 cm L) at 0.43 mL/min absolute ethanol/ *iso*-hexane (75:25))

Retention time: 11.4 minutes

Optical purity: 99.9% e.e (no enantiomer B present)

^{1}H NMR (CD_3OD) δ 1.60 (s, 3H), 4.84 (m obscured by water singlett, 1H), 7.50 (d, 2H, *J*= 8 Hz), 7.62 (d, 2H; *J*= 8 Hz) and 7.79 (m, 4H) ppm.

Enantiomer B ("late" fractions)

Yield: 0.040 g white solid

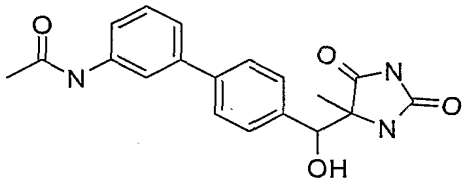
Chiral chromatography (Chiralpak AD-H (0.45 cm I.D x 25 cm L) at 0.43 mL/min absolute ethanol/ *iso*-hexane (75:25))

Retention time: 18.0 minutes

Optical purity: 99.0% e.e (0.50% of enantiomer A present)

^{1}H NMR (CD_3OD) δ 1.60 (s, 3H), 4.84 (m obscured by water singlett, 1H), 7.50 (d, 2H, *J*= 8 Hz), 7.62 (d, 2H; *J*= 8 Hz) and 7.79 (m, 4H) ppm.

***N*–(*4'*-(hydroxy-(4-methyl-2,5-dioxoimidazolidin-4-yl)-methyl)biphenyl-3-yl)acetamide**



Chromatographic resolution :

0.040 g of diastereomerically pure *N*–(*4'*-(hydroxy-(4-methyl-2,5-dioxoimidazolidin-4-yl)-methyl)biphenyl-3-yl)acetamide was dissolved in 224 mL absolute ethanol/ *iso*-hexane (71:29) and separated as discribed above with absolute ethanol/ *iso*-hexane (50:50) at 6.0 mL/min as eluant.

Enantiomer A ("early" fractions)

Yield: 0.019 g white solid

Chiral chromatography (Chiralpak AD-H (0.45 cm I.D x 25 cm L) at 0.43 mL/min absolute ethanol/ *iso*-hexane (50:50))

Retention time: 10.4 minutes

Optical purity: 99.9% e.e (no enantiomer B present)

^{1}H NMR (CD_3OD) δ 1.60 (s, 3H), 2.14 (s, 3H), 4.82 (m obscured by water singlett, 1H), 7.33 (m, 1H), 7.36 (t, 1H, *J*= 8 Hz), 7.44 (d, 2H, *J*= 8 Hz), 7.50 (m, 1H), 7.54 (d, 2H; *J*= 8 Hz) and 7.82 (m, 1H) ppm.

Enantiomer B ("late" fractions)

Yield: 0.018 g white solid

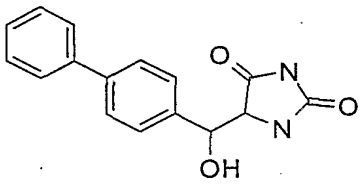
Chiral chromatography (Chiralpak AD-H (0.45 cm I.D x 25 cm L) at 0.43 mL/min absolute ethanol/ *iso*-hexane (50:50))

Retention time: 14.8 minutes

Optical purity: 99.6% e.e (0.20% of enantiomer A present)

^{1}H NMR (CD_3OD) δ 1.60 (s, 3H), 2.14 (s, 3H), 4.82 (m obscured by water singlett, 1H), 7.33 (m, 1H), 7.36 (t, 1H, *J*= 8 Hz), 7.44 (d, 2H, *J*= 8 Hz), 7.50 (m, 1H), 7.54 (d, 2H; *J*= 8 Hz) and 7.82 (m, 1H) ppm.

5-(Biphenyl-4-yl-hydroxy-methyl)-imidazolidine-2,4-dione.



Chromatographic resolution:

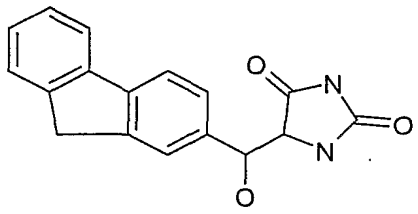
Separation was made on a Gilson HPLC system (column: CHIRALPAK AD, 2.0x25 cm. Solvent: isoHexane/EtOH = 25/75. Flow=6.0mL/min. UV=254nm. Inj volume=3.0 mL). 24 mg of the racemic material was dissolved in 24mL of isoHexane/EtOH = 25/75. The two enantiomers with Rt=17.72min and 20.47min was collected and solvent was removed by evaporation. Analysed for enantiomeric purity using the following Gilson HPLC system (column: CHIRALPAK AD, 0.46x25 cm. Solvent: isoHexane/EtOH = 25/75.

Flow=0.5mL/min. UV=254nm).Faster enantiomer: 9mg, Rt=10.12 min, ee=99.9%. Slower enantiomer: 7mg, Rt=11.78 min, ee=99.2%.

EXAMPLE 35

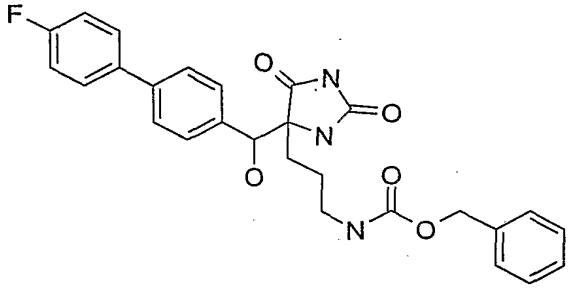
The following compounds where prepared by a method analogous to that described in Example 24.

5-[(9 H-Fluoren-2-yl)-hydroxy-methyl]-imidazolidine-2,4-dione



APCI-MS m/z: 277 [MH+ - H2O]

(3-{4-[(4'-Fluoro-biphenyl-4-yl)-hydroxy-methyl]-2,5-dioxo-imidazolidin-4-yl}-propyl)-carbamic acid benzyl ester

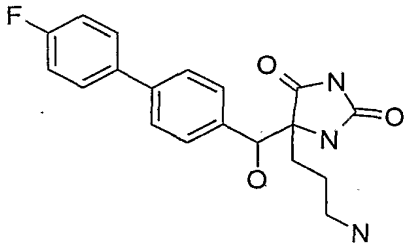


1H NMR (400 MHz, DMSO-d6): δ 10.20 (1H, s); 8.53 (1H,d, J=4.01Hz); 8.01 (1H, s); 7.69 (2H, m); 7.56 (2H, d, J=8.39Hz), 7.30 (9H, m), 5.90 (1H, d, J=4.20Hz), 4.99 (2H, s) 4.64 (1H, d, J=4.20Hz); 2.98(2H, m), 1.97 (1H, m), 1.72 (1H, m), 1.42 (1H, m), 1.22 (1H, m).

APCI-MS m/z: 492.2 [MH^+].

5-(3-Amino-propyl)-5-[(4'-fluoro-biphenyl-4-yl)-hydroxy-methyl]-imidazolidine-2,4-dione

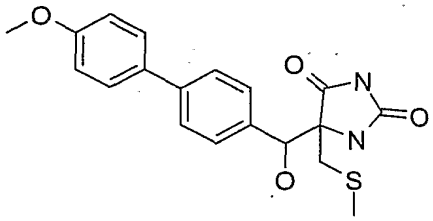
Prepared from above (3-{4-[(4'-Fluoro-biphenyl-4-yl)-hydroxy-methyl]-2,5-dioxo-imidazolidin-4-yl}-propyl)-carbamic acid benzyl ester by a standard method known for those skilled in the art.



APCI-MS m/z: 358.1 [MH^+].

5-[Hydroxy-(4'methoxy-biphenyl-4-yl)-methyl]-5-methylsulfanylmethyl-imidazolidine-2,4-dione

Prepared from 4'-methoxy-biphenyl-4-carbaldehyde (Table 3, Method B) and 5-methylsulfanylmethyl-imidazolidine-2,4.dione (Table 2, Method A) according to Method C, Example 24.

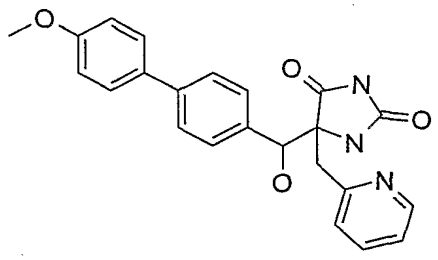


1H NMR (400 MHz, DMSO-d6): δ 10.25 (1H, s); 8.16 (1H, s); 7.59 (2H, d, J=8.77Hz,), 7.53(2H, d, J=8.20Hz); 7.31 (2H, d, J=8.20Hz); 6.99 (2H, d, J=8.77Hz); 5.98 (1H, d, J=4.20Hz); 4.71 (1H, d, J=4.01Hz); 3.77 (3H, s); 3.16 (1H, d, J=14.31Hz9, 2.92(1H, d, J=14.31Hz), 2.11 (3H, s).

APCI-MS m/z: 373.1 [MH^+]

5-[Hydroxy-(4'-methoxy-biphenyl-4-yl)-methyl]-5-pyridin-2-ylmethyl-imidazolidine-2,4-dione

Prepared from 4'-methoxy-biphenyl-4-carbaldehyde (Table 3, Method B) and commercially available 5-pyridin-2-ylmethyl-imidazolidine-2,4.dione according to Method C, Example 24.

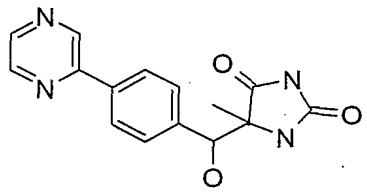


1H NMR (400 MHz, DMSO-d6): δ 10.00 (1H, s); 8.53 (1H,d, J=4.01Hz); 8.13 (1H, s,); 7.91 (1H, s); 7.58 (2H, m); 7.53 (2H, m); 7.38 (4H, m), 7.00 (2H, m), 6.11 (1H, s) 4.81 (1H, s); 3.48(2H, m).

APCI-MS m/z: 404.3 [MH^+].

5-[Hydroxy-(4-pyrazin-2-yl-phenyl)-methyl]-5-methyl-imidazolidine-2,4-dione

Prepared from commercially available 4-pyrazin-2-yl-benzaldehyde and 5-methyl-hydantoin according to Method C, Example 24.



APCI-MS m/z: 299 [MH^+].

5-{3-[4-(5-Chloro-pyridin-2-yloxy)-phenyl]-1-hydroxy-propyl}-5-methyl-imidazolidine-2,4-dione

3-[4-(5-Chloro-pyridin-2-yloxy)-phenyl]-propan-1-ol

3-(4-Hydroxyphenyl)-propanol (768.5, 5.05 mmol), 2,5-dichloro-pyridine (934.8 mg, 6.32 mmol), cesium carbonate (2.48 g, 7.60 mmol) mixed in N-methyl-pyrollidone (10 ml) was stirred and heated (100 °C) for 20 hours. The flask was cooled and the content was partitioned between ethyl acetate (100 ml), di-tertbutylether (100 ml) and water (300 ml). The organic phase was washed with water (3 X 30 ml). Evaporation afforded the crude title compound (1.502 g, 5.70 mmol) as a yellow oil in 113 % yield. Pure according to TLC analysis.

APCI-MS m/z: 264 [MH^+]

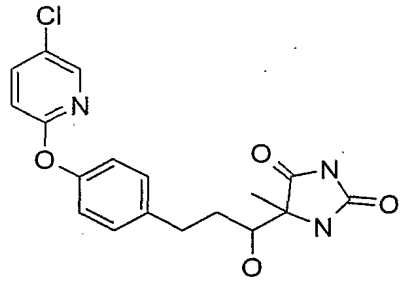
3-[4-(5-Chloro-pyridin-2-yloxy)-phenyl]-propionaldehyde

3-[4-(5-Chloro-pyridin-2-yloxy)-phenyl]-propan-1-ol (267 mg, 1.0 mmol) and pyridinium chloro chromate (302 mg, 1.4 mmol) was stirred in dichloromethan (20 ml, molecular sieve dried) for 2 hours. Flash chromatography (SiO_2, dichloromethan/methanol: gradient to 100/5) afforded the title compound (169 mg, 0.65 mmol) as a oil in 65 % yield.

APCI-MS m/z: 262 [MH^+]

5-{3-[4-(5-Chloro-pyridin-2-yloxy)-phenyl]-1-hydroxy-propyl}-5-methyl-imidazolidine-2,4-dione

3-[4-(5-Chloro-pyridin-2-yloxy)-phenyl]-propionaldehyde and commercially available 5-methyl-hydantoin was utilized for synthesis of the title compound according to Method C, Example 24.



APCI-MS m/z: 376.0 [MH^+].

5-{[4-(5-Chloro-pyridin-2-yloxy)-phenyl]-hydroxy-methyl}-5-methyl-imidazolidine-2,4-dione

4-(5-Chloro-pyridin-2-yloxy)-benzaldehyde

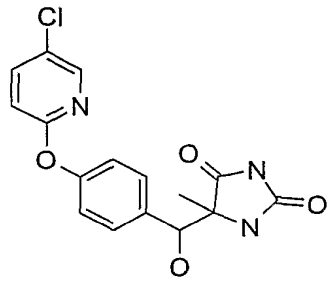
4-Hydroxy-benzaldehyde (620.9 mg, 5.08 mmol), cesiumcarbonate (2.6 g, 7.98 mmol) and 2,5-dikloropyridine (947 mg, 6.40 mmol) mixed in N-methyl-pyrollidone (10 ml) was strirred and heated (75 °C) for 16 hours. LCMS analysis indicated formation of product in a minor amount. Further reaction at elevated temperature (150 °C) for additional six hours produced increased formation of product. The flask was cooled and the content was partitioned between ethyl acetate (100 ml), ether (100 ml) and water (200 ml). The organic phase was washed with water (3 X 30 ml). Evaporation and flash chromatography (SiO_2, dichloromethan/methanol: gradient to 100/4) afforded 4-(5-chloro-pyridin-2-yloxy)-benzaldehyde (181 mg, 0.77 mmol) in 15.2 % yield.

1H NMR (400 MHz, DMSO-d6): δ 9.98 (1H, s);8.27 (1H, d);8.04 (1H, dd);7.97 (2H, d);7.35 (2h, d);7.23 (1H, d).

APCI-MS m/z: 234 [MH^+]

5-{[4-(5-Chloro-pyridin-2-yloxy)-phenyl]-hydroxy-methyl}-5-methyl-imidazolidine-2,4-dione

4-(5-Chloro-pyridin-2-yloxy)-benzaldehyde and commercially available 5-methyl-hydantoin was utilized for synthesis of the title compound according to Method C, Example 24.

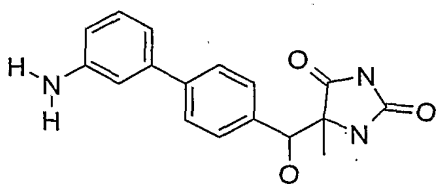


APCI-MS m/z: 348 [MH^+].

EXAMPLE 36

5-[(3'-Amino-biphenyl-4-yl)- hydroxy- methyl]-5-methyl-imidazolidine-2,4-dione

Prepared from 5-[Hydroxy-(3'-nitro-biphenyl-4-yl)-methyl]-5-methyl-imidazolidine-2,4-dione described in Example 31 by by a standard synthetic method well-known for those skilled in the art (Pd (0) catalysed hydrogenation in ethanol).



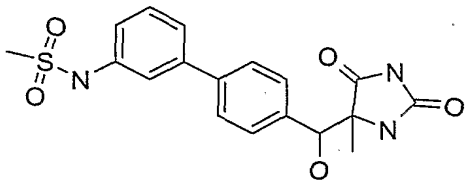
APCI-MS m/z: 312.1 [MH^+]

EXAMPLE 37

The following compounds where prepared according to the protocol used for synthesis of N-{4'-[hydroxy-(4-methyl-2,5-dioxo-imidazolin-4-yl)-methyl]-biphenyl-3-yl}-methansulfonamide described below.

N-{4'-[hydroxy-(4-methyl-2,5-dioxo-imidazolin-4-yl)-methyl]-biphenyl-3-yl}-methansulfonamide

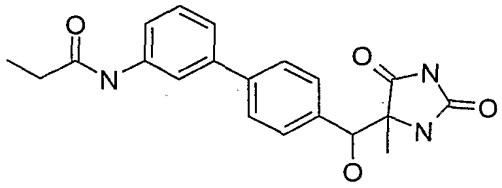
Methanesulfonyl chloride (10ul, 0.165mmol) was added dropwise to a solution of 5-[(3'-Amino-biphenyl-4-yl)- hydroxy- methyl]-5-methyl-imidazolidine-2,4-dione (41 mg, 0.132mmol) in pyridine (1 ml). The resulting mixture was stirred for 6 hours at ambient temperature. Water (15 ml) was added and the aqueous mixture was extracted with EtOAc (3 x 10 ml). The combined EtOAc extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. Preparative HPLC on a Chromasil C18 column with acetonitrile/water (0.1% trifluoroacetic acid), afforded the 40mg (80% yield) of the title compound N-{4'-[hydroxy-(4-methyl-2,5-dioxo-imidazolin-4-yl)-methyl]-biphenyl-3-yl}-methansulfonamide.



1H NMR (400 MHz, DMSO-d6): δ 10.17 (1H, s); 9.79 (1H,s); 8.10 (1H, s,); 7.57 (2H, d, J=8.39Hz); 7.40 (5H, m); 7.19 (1H, m); 7.25 (2H, d, J=8.39Hz); 7.20 (1H, m); 5.92 (1H, m); 4.65 (1H, s); 3.01 (3H, s); 1.42 (3H, s,).

APCI-MS m/z: 390.1 [MH^+]

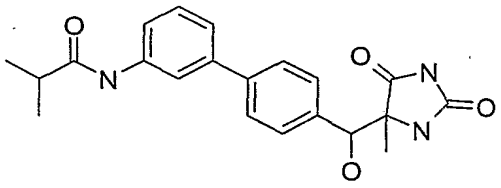
***N*-{4'-[hydroxy-(4-methyl-2,5-dioxo-imidazolin-4-yl)-methyl]-biphenyl-3-yl}-propionate**



1H NMR (400 MHz, DMSO-d6): δ 10.17 (1H, s); 9.90 (1H,s); 8.09 (1H, s,); 7.90 (1H, s); 7.51 (3H, m); 7.32 (4H, m); 5.92 (1H, d, J=4.39Hz); 4.65 (1H, d, J=4.39Hz); 2.32 (1H, q, J=7.44Hz); 1.42(3H, s); 1.08 (3H, t, J=7.53Hz).

APCI-MS m/z: 368.1 [MH^+].

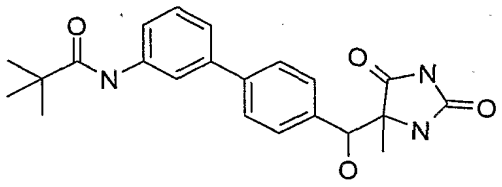
***N*-{4'-[hydroxy-(4-methyl-2,5-dioxo-imidazolin-4-yl)-methyl]-biphenyl-3-yl}-isobutyramide**



1H NMR (400 MHz, DMSO-d6): δ 10.15 (1H, s); 9.87 (1H,s); 8.09 (1H, s,); 7.92 (1H, s); 7.52 (3H, m); 7.33 (4H, m); 5.92 (1H, d, J=4.39Hz); 4.65 (1H, d, J=4.39Hz); 2.59 (1H, m); 1.42(3H, s); 1.10 (6H, d, J=6.87Hz).

APCI-MS m/z: 382.1 [MH^+].

***N*-{4'-[hydroxy-(4-methyl-2,5-dioxo-imidazolin-4-yl)-methyl]-biphenyl-3-yl}-2,2-dimethylpropionamide**

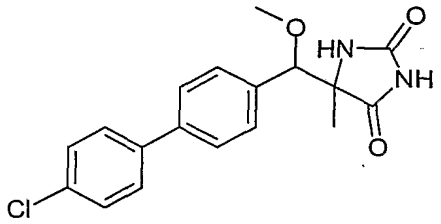


1H NMR (400 MHz, DMSO-d6): δ 10.15 (1H, s); 9.23 (1H,s); 8.09 (1H, s,); 7.93 (1H, s); 7.58 (3H, m); 7.33 (4H, m); 5.91 (1H, d, J=4.39Hz); 4.65 (1H, d, J=4.39Hz); 1.42(3H, s); 1.22 (9H, s).

APCI-MS m/z: 396.2 [MH^+].

EXAMPLE 38

5-[(4'-Chlorobiphenyl-4-yl)methoxymethyl]-5-methylimidazolidine-2,4-dione



4-Chloro-4'-(2-nitropropenyl)biphenyl

4-(4-Chlorophenyl)benzaldehyde (0.66 g, 3.0 mmoles), nitroethane (2 mL), ammonium carbonate (3.5 g) and glacial acetic acid (17 mL) was stirred under nitrogen at 82°C for 20 hours. Volatiles were evaporated, the wellow residue was taken up in ether and washed once with water. The aqueous phase was separated and washed once with ether. The combined organic phases were washed with water and brine, dried over anhydrous sodium

sulfate, filtered and concentrated with silica (3 g) by rotary evaporation. The dry residue was applied on a silica column. Elution with ethyl acetate/n-heptane (1:20) through (1:8) gave 0.50 g (61% yield) of the title compound as wellow crystalls. Mp. 113.8-114.3°C (uncorrected).

FT-IR (ATR) ν 1647 (w), 1504 (str), 1484 (str), 1320 (v str), 812 (str) cm^{-1}.

^1H NMR (300MHz, $CDCl_3$) δ 2.50 (d, 3H, J= 1 Hz), 7.44 (d, 2H, J= 9 Hz), 7.52 (d, 2H, J= 9 Hz), 7.55 (d, 2H, J= 9 Hz), 7.65 (d, 2H, J= 9 Hz) and 8.12 (br s, 1H) ppm.

^{13}C NMR (100MHz, $CDCl_3$) δ 14.2, 127.2, 128.2, 129.1, 130.5, 131.5, 132.9, 134.1, 138.1, 141.3 and 147.6 ppm.

4-Chloro-4´-(1-methoxy-2-nitropropyl)biphenyl

A mixture of 4-chloro-4´-(2-nitropropenyl)biphenyl (0.39 g, 1.3 mmoles), sodium methoxide (4.0 mmoles; freshly prepared from 0.091 g of sodium and dry methanol) and anhydrous 1,2-dimethoxyethane (3.0 mL) was stirred under nitrogen at 22°C for three hours, acidified with 10% acetic acid in methanol (4 mL), concentrated to dryness by rotary evaporation and then taken up in ethyl acetate and water. The aqueous phase was separated and washed once with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated with silica (3 g) by rotary evaporation. The dry residue was applied on a silica column. Elution with dichloromethane/n-heptane (1:3) through (1:1) gave 0.40 g (95% yield) of the title compound as a white solid.

FT-IR (ATR) ν 1552 (v str), 1485 (str), 1092 (str), 814 (str) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, 1.3 H, J= 7 Hz) 1.56 (d, 1.7 H, J= 7 Hz), 3.22 (s, 1.2 H), 3.32 (s, 1.8 H), 4.56 (d, 1.2 H, J= 10 Hz), 4.63 (m_c, 1.8 H), 4.76 (m_c, 1.2 H), 4.88 (d, 1.8 H, J= 5 Hz) and 7.38-7.62 (m´s, 8 H) ppm. ^{13}C NMR (100MHz, $CDCl_3$) δ 13.0, 16.3, 57.0, 57.7, 83.5, 84.8, 86.9, 87.5, 127.3, 127.5, 128.3, 129.0, 129.1, 132.7, 133.7, 133.9, 135.1, 135.9, 138.7, 138.8, 140.4, 140.9 ppm (diastereomeric signals).

1-(4′-Chlorobiphenyl-4-yl)-1-methoxypropan-2-one

A mixture of 4-chloro-4′-(1-methoxy-2-nitropropyl)biphenyl (0.123 g, 0.40 mmoles), dry dichloromethane (2.8 mL) and finely ground 3Å molecular seeves (0.040 g) under argon was cooled on an ice bath. Tetrapropylammonium perruthenate (0.170 g, 0.48 mmoles) was added in a portionwise manner to the cold, stirred mixture. When the addition was completed, the ice bath was removed and the mixture was stirred at 22°C for 4.0 hours. Diethyl ether (30 mL) was added and the resulting dark suspension was filtered through Celite. The clear filtrate was concentrated with silica (4 g) by rotary evaporation. The dry residue was applied on a silica column. Elution with dichloro-methane/n-heptane (1:2) through (2:1) gave 0.052 g (47% yield) of the title compound as a white solid. FT-IR (ATR) ν 1716 (v str), 1485 (str), 1093 cm $^{-1}$ (v str).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16 (s, 3 H) 3.42 (s, 3 H), 4.69 (s, 1 H), 7.40 (d, 2 H, J= 9 Hz), 7.46 (d, 2 H, J= 8 Hz), 7.51 (d, 2 H, J= 9 Hz) and 7.56 (d, 2 H, J= 8 Hz) ppm. ^{13}C NMR (100MHz, $CDCl_3$) δ 25.1, 57.3, 89.1, 127.2, 127.4, 128.2, 128.8, 133.5, 135.1, 138.8, 140.1 and 206.4 ppm

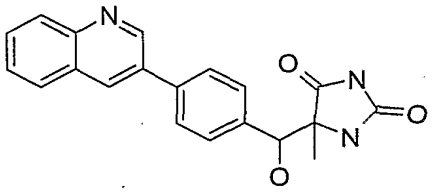
5-[(4′-Chlorobiphenyl-4-yl)methoxymethyl]-5-methylimidazolidine-2,4-dione

1-(4′-Chlorobiphenyl-4-yl)-1-methoxypropan-2-one (0.051 g, 0.19 mmoles), ammonium carbonate (0.089 g, 0.93 mmoles), potassium cyanide (0.025 g, 0.37 mmoles; CAUTION!) and 50% ethanol in water (1.4 mL) were stirred in a sealed vial (4.5 mL) at 87°C (oil bath temperature) for 19 hours. The solvent was evaporated, water was added to make a volume of approx. 20 mL, pH was adjusted to 3 with glacial acetic and the crude product was taken up in ethyl acetate (50 mL). The organic phase was washed once with brine, dried over anhydrous sodium sulfate, filtered and concentrated by rotary evaporation to afford 0.065 g (100% yield) of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.06 (s, 2 H), 1.43 (s, 1 H), 3.07 (s, 2 H), 3.17 (s, 1 H), 4.33 (s, 0.7 H), 4.34 (s, 0.3 H), 7.30-7.75 (m′s, 8.7 H), 8.24 (br s, 0.3 H), 10.26 (br s, 0.3 H) and 10.56 (br s, 0.7 H) ppm. ^{13}C NMR (100MHz, DMSO-d_6) δ 20.2, 21.1, 56.6, 57.0, 65.5, 66.2, 84.2, 84.9, 125.8, 126.1, 128.20, 128.22, 128.74, 128.76, 128.79, 128.9, 132.2, 135.3, 135.4, 138.2, 138.3, 138.3, 138.4, 156.1, 156.9, 175.9 and 177.1 ppm (diastereomeric signals).

EXAMPLE 39

5-[Hydroxy-(4-quinolin-3-yl-phenyl)-methyl-imidazolidine-2,4-dione

This compound was synthesised according to *J. Org. Chem.* **2001,** 66, 1500-1502 from commercially available 3-bromo-quinoline and 5-[Hydroxy-(4-iodo-phenyl)-methyl]-imidazolidine-2,4-dione described above.

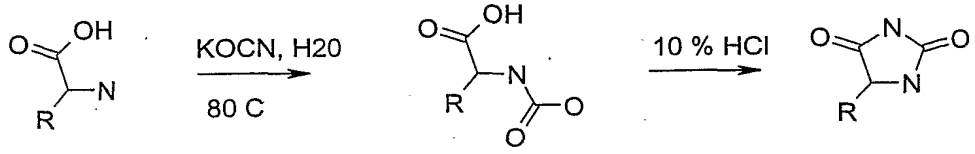


APCI-MS m/z: 348.2 [MH^+]

EXAMPLES 40 TO 61: Preparation of starting materials

According to Scheme 4 below, the hydantoins **5** were prepared in two steps from general amino acids **3** with isolation of the intermediates **4**.

Scheme 4



3 **4** **5**

Table 1 lists some of the starting materials, **5**, that were synthesized. The general method of preparation was as follows. A slurry of amino acid **3** (25 mmol) and potassium cyanate (5.1 g, 63 mmol) in water (75 ml) was heated at 80°C for approximately 1 hour. The clear solution was cooled to 0°C and acidified to approximately pH 1 with concentrated hydrochloric acid (aq). The resulting white precipitate **4** was heated at reflux for 0.5-1 hour and then cooled on ice. In some instances full conversion was not reached

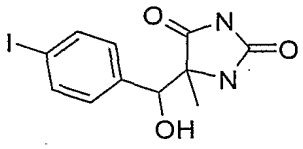
after 1 hour heating. In these cases the crude material was treated under the same protocol again. The white solid was filtered, washed with water, dried and analysed by HNMR and LCMS.

Table 1: Starting materials

Compounds **5** in Scheme 4	Yield (%)	APCI-MS m/z: [MH^+]
5-(4-Chloro-benzyl)-imidazolidine-2,4-dione	87	224.9
[3-(2,5-Dioxo-imidazolidin-4-yl)-propyl]-carbamic acid benzyl ester	50	292.0
5-Isobutyl-imidazolidine-2,4-dione	85	157.0
5-Methylsulfanylmethyl-imidazolidine-2,4-dione	45	161.0
5-sec-Butyl-imidazolidine-2,4-dione	52	157.0
5-(2-Hydroxy-ethyl)-imidazolidine-2,4-dione	36	

EXAMPLE 40

5-[Hydroxy-(4-iodo-phenyl)-methyl]-5-methyl-imidazolidine-2,4-dione



4-Iodo-benzaldehyde (9.280 g, 40.0 mmol), 5-methyl-hydantoin (4.564 g, 40.0 mmol) and 45 % aqueous trimethylamine (6.40 ml, 40.0 mmol) was heated at reflux in ethanol (60 ml) and water (40 ml) for 20 hours under an atmosphere of nitrogen. A white precipitate was formed. After cooling at room temperature for approximately 15 minutes the precipitate was collected by filtration, washed sequentially with ethanol (50%, 50 ml), water (50 ml)

and diethyl ether (50 ml). Drying by air suction afforded the title compound (7.968 g, 23.0 mol) in 57.5 % yield as white solid in form of a pure diastereoisomer.

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.19 (1H, s); 8.08 (1H, s); 7.64 (2H, d, J = 8.6Hz); 7.07 (2H, d, J = 8.4 Hz); 5.98 (1H, d, J = 4.5 Hz); 4.57 (1H, d, J = 4.3 Hz); 1.40 (3H, s). APCI-MS m/z: 346.9 [MH^+].

Chromatographic resolution:

A portion of 0.158 g diastereomerically pure 5-(hydroxy-(4-iodophenyl)-methyl)-5-methyl-imidazolidine-2,4-dione was dissolved in 205 mL absolute ethanol/ *iso*-hexane (50:50) and filtered through a 0.45 μm nylon filter. Volumes of 5.0 mL were injected repeatedly on a chiral column (Chiralpak AD-H (2 cm ID x 25 cm L)) connected to a UV-detector (254 nm) and fraction collector. Separation was performed with absolute ethanol/ *iso*-hexane (50:50) as eluant at 6.0 mL/min flow and the pure enantiomers eluted. Fractions containing the same enantiomer were combined, concentrated and assessed for optical purity by chiral chromatography (see below).

Enantiomer A ("early" fractions)

Yield: 0.068 g white flakes

Chiral chromatography (Chiralpak AD-H (0.45 cm I.D x 25 cm L) at 0.43 mL/min absolute ethanol/ *iso*-hexane (50:50))

Retention time: 10.5 minutes

Optical purity: 99.9% e.e (no enantiomer B present)

Enantiomer B ("late" fractions)

Yield: 0.071 g white flakes

Chiral chromatography (Chiralpak AD-H (0.45 cm I.D x 25 cm L) at 0.43 mL/min absolute ethanol/ *iso*-hexane (50:50))

Retention time: 12.2 minutes

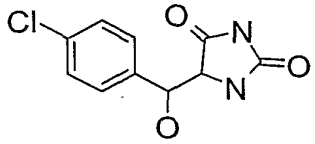
Optical purity: 99.6% e.e (0.24% of enantiomer B present)

The NMR spectra of the pure enantiomers matched that of the pure diastereoisomer.

The following Examples were prepared following the procedure in Example 40. If not otherwise indicated, final compounds represent a mixture of four stereoisomers. Column chromatography was used for final purification or for separation of diastereoisomers.

EXAMPLE 41

5-[(4-Chloro-phenyl)-hydroxy-methyl)]-imidazolidine-2,4-dione



Diastereoisomer A

^{1}H NMR (400 MHz, DMSO-d6): 10.32 (1H, s); 8.07 (1H, s); 7.37 (2H, d, J = 8.5 Hz); 7.30 (2H, d, J = 8.5 Hz); 5.94 (1H, d, J = 3.9 Hz); 4.92 (1H, t, J = 3.2 Hz); 4.35 (1H, dd, J = 3.1,1.0Hz).

^{13}C NMR (400 MHz, DMSO-d6): 173.00; 157.36; 138.41; 131.98; 128.86; 127.52; 71.65; 63.88.

APCI-MS m/z: 241 [MH+].

Diastereoisomer B

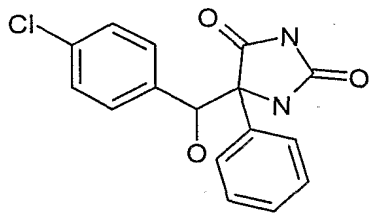
^{1}H NMR (400 MHz, DMSO-d6): 10.53 (1H, s); 7.54 (1H, s); 7.42-7-37 (4H, m); 5.83 (1H, d, J = 5.6 Hz); 4.91 (1H, dd, J = 5.6, 2.6 Hz); 4.23 (1H, dd, J = 2.6,1.5 Hz).

^{13}C NMR (400 MHz, DMSO-d6): 173.97; 158.04; 140.62; 131.67; 128.15; 127.89; 70.08; 63.93.

APCI-MS m/z: 241 [MH+].

EXAMPLE 42

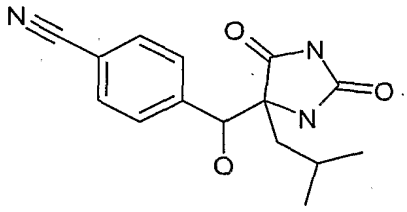
5-[(4-Chloro-phenyl)-hydroxy-methyl]-5-phenyl-imidazolidine-2,4-dione



APCI-MS m/z: 317.1 [MH+].

EXAMPLE 43

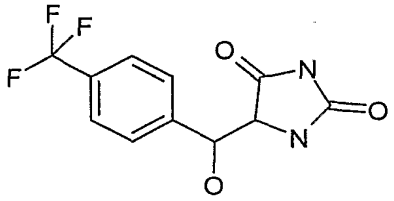
5-[(4-Cyano-phenyl)-hydroxy-methyl]-5-isobutyl-imidazolidine-2,4-dione



APCI-MS m/z: 288.1 [MH+].

EXAMPLE 44

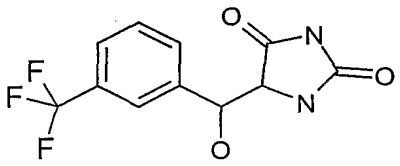
5-[(4-Trifluoromethyl-phenyl)-hydroxy-methyl]-imidazolidine-2,4-dione



APCI-MS m/z: 275.1 [MH+].

EXAMPLE 45

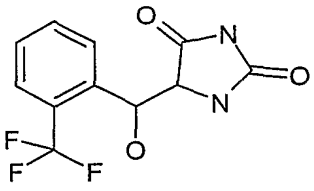
5-[(3-Trifluoromethyl-phenyl)-hydroxy-methyl]-imidazolidine-2,4-dione



APCI-MS m/z: 275.2 [MH+].

EXAMPLE 46

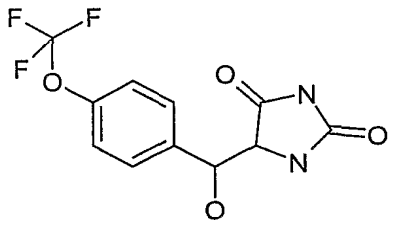
5-[(2-Trifluoromethyl-phenyl)-hydroxy-methyl]-imidazolidine-2,4-dione



APCI-MS m/z: 275.1 [MH+].

EXAMPLE 47

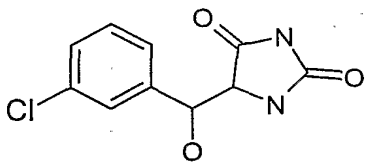
5-[(4-Trifluoromethoxy-phenyl)-hydroxy-methyl]-imidazolidine-2,4-dione



APCI-MS m/z: 291.3 [MH+].

EXAMPLE 48

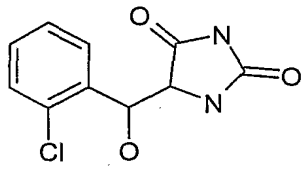
5-[(3-Chloro-phenyl)-hydroxy-methyl]-imidazolidine-2,4-dione



APCI-MS m/z: 241.0 [MH+].

EXAMPLE 49

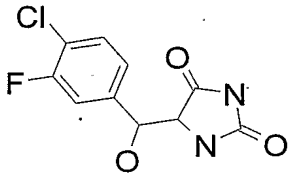
5-[(2-Chloro-phenyl)-hydroxy-methyl]-imidazolidine-2,4-dione



APCI-MS m/z: 241.0 [MH+].

EXAMPLE 50

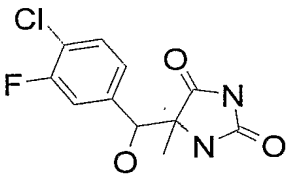
5-[(4-Chloro-3-fluoro-phenyl)-hydroxy-methyl]-imidazolidine-2,4-dione



APCI-MS m/z: 259.0 [MH+]

EXAMPLE 51

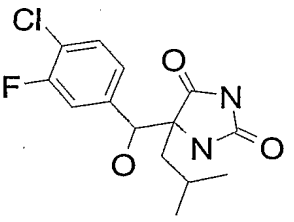
5-[(4-Chloro-3-fluoro-phenyl)-hydroxy-methyl]-5-methyl-imidazolidine-2,4-dione



APCI-MS m/z: 272.9 [MH+]

EXAMPLE 52

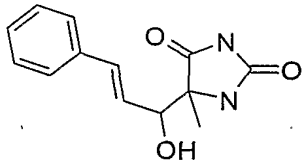
5-[(4-Chloro-3-fluoro-phenyl)-hydroxy-methyl]-5-isobutyl-imidazolidine-2,4-dione



APCI-MS m/z: 315.9 [MH+]

EXAMPLE 53

5-(1-Hydroxy-3-phenyl-allyl)-5-methyl-imidazolidine-2,4-dione

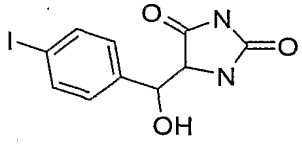


^{1}HNMR (400 MHz, DMSO-d_6): δ 10.45 (1H, s); 7.88 (1H, s); 7.38-7.22 (5H, m); 6.54 (1H, d , J = 16.1 Hz); 6.22 (1H, dd, J = 7.3, 7.6 Hz); 5.56 (1H, d, J = 4.5 Hz); 4.09 (1H, d, J = 3.6, 4.5 Hz); 1.27 (3H, s).

APCI-MS m/z: 247.1 [MH^+].

EXAMPLE 54

5-[Hydroxy-(4-iodo-phenyl)-methyl]-imidazolidine-2,4-dione

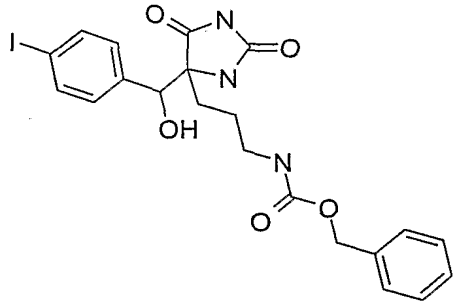


^{1}HNMR (300 MHz, DMSO-d_6): δ 10.32 (1H, s); 8.06 (1H, s); 7.66 (2H, d, J = 8.1 Hz); 7.10 (2H, d, J = 8.3 Hz); 5.91 (1H, d, J = 3.9 Hz); 4.87 (1H, t, J = 2.7 Hz); 4.34 (1H, d, J = 2.5 Hz).

APCI-MS m/z: 333.1 [MH^+].

EXAMPLE 55

(3-{4-[Hydroxy-(4-iodo-phenyl)-methyl]-2,5-dioxo-imidazolidin-4-yl}-propyl)-carbamic acid benzyl ester

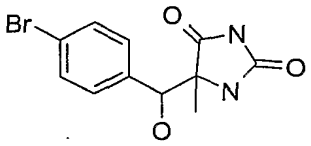


APCI-MS m/z: 524.1 [MH^+].

EXAMPLE 56

5-[(4-Bromo-phenyl)-hydroxy-methyl]-5-methyl-imidazolidine-2,4-dione

Produced by aldol condensation of 4-bromo-benzaldehyde and 5-Methyl-imidazolidine-2,4-dione.



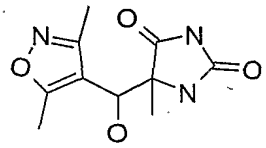
^1H NMR (400 MHz, DMSO-d6): δ 10.18 (1H, s); 8.08 (1H, s); 7.46 (2H, d, J=8.4Hz); 7.20 (2H, d, J=8.4 Hz); 5.99 (1H, d, J=4.4 Hz); 4.59 (1H, d, 3.81 Hz); 1.39 (3H, s).

APCI-MS m/z: 298.9 [MH^+]

EXAMPLE 57

5-[(3,5-Dimethyl-isoxazol-4-yl)-hydroxy-methyl]-5-methyl-imidazolidine-2,4-dione

Produced by aldol condensation of 3,5-dimethyl-isoxazole-4-carbaldehyde and 5-Methyl-imidazolidine-2,4-dione.

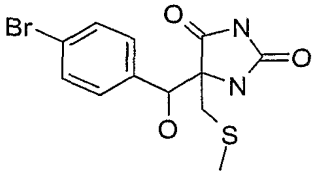


APCI-MS m/z: 240 [MH^+]

EXAMPLE 58

5-[(4-Bromo-phenyl)-hydroxy-methyl]-5-methylsulfanylmethyl-imidazolidine-2,4-dione

Produced by aldol condensation of 4-bromo-benzaldehyde and 5-methylsulfanylmethyl-imidazolidine-2,4-dione.

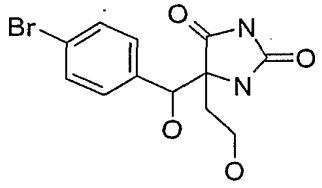


APCI-MS m/z: 347.1 [MH^+]

EXAMPLE 59

5-[(4-Bromo-phenyl)-hydroxy-methyl]-5-(2-hydroxy-ethyl)-imidazolidine-2,4-dione

Produced by aldol condensation of 4-bromo-benzaldehyde and 5-(2-hydroxy-ethyl)-imidazolidine-2,4-dione.

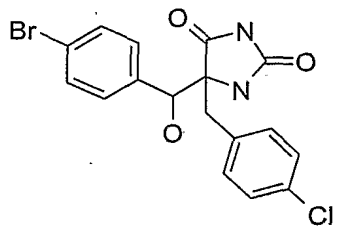


APCI-MS m/z: 311.2 [MH^+ -H_2O]

EXAMPLE 60

5-[(4-Bromo-phenyl)-hydroxy-methyl]-5-(4-chloro-benzyl)-imidazolidine-2,4-dione

Produced by aldol condensation of 4-bromo-benzaldehyde and 5-(4-chloro-benzyl)-imidazolidine-2,4-dione.

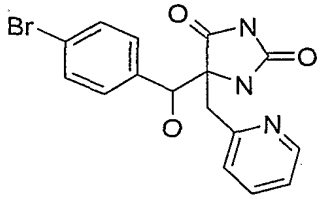


APCI-MS m/z: 411 [MH^+]

EXAMPLE 61

5-[(4-Bromophenyl)hydroxy-methyl]-5-pyridine-2-ylmethyl-imidazolidine-2,4-dione

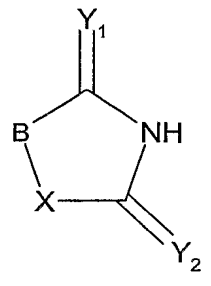
Produced by aldol condensation of 4-bromo-benzaldehyde and 5-pyridine-4-ylmethyl-imidazolidine-2,4-dione.



APCI-MS m/z: 378.1 [MH^+]

CLAIMS:
What we claim is:

1. A metalloproteinase inhibitor compound or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof for use in the treatment of a disease or condition mediated by one or more metalloproteinase enzymes wherein the metalloproteinase inhibitor compound comprises a metal binding group and one or more other functional groups or side chains characterised in that the metal binding group has the formula (I)



(I)

wherein **X** is selected from NR1, O, S;

B is C or CH, and is the point of attachment of the one or more other functional groups or side chains;

Y1 and **Y2** are independently selected from O, S;

R1 is selected from H, alkyl, haloalkyl.

2. A metalloproteinase inhibitor compound or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof as claimed in claim 1 which comprises a metal binding group of formula (I) wherein X is NR1; at least one of Y1 and Y2 is O; R1 is H, (C1-6)alkyl or halo(C1-6)alkyl.

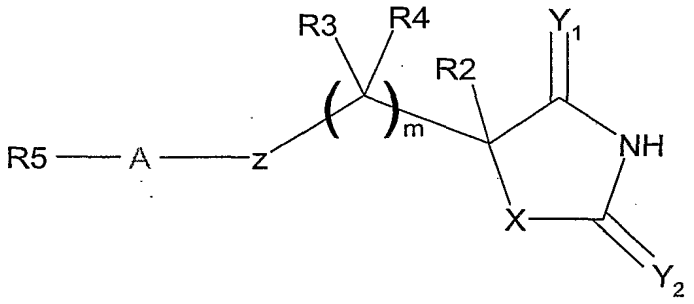
3. A metalloproteinase inhibitor compound or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof as claimed in claim 1 wherein the metal binding group of formula (I) is a -5 substituted 1-H,3-H-imidazolidine-2,4-dione.

4. A metalloproteinase inhibitor compound or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof as claimed in claim 1 for use in the treatment of a disease or condition mediated by one or more matrix metalloproteinase enzymes.

5. A metalloproteinase inhibitor compound or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof as claimed in claim 4 for use in the treatment of a disease or condition mediated by one or more enzymes selected from MMP12, MMP9, MMP13, MMP8, MMP3.

6. A metalloproteinase inhibitor compound or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof as claimed in claim 1 wherein the metalloproteinase inhibitor compound is either:

(a) a compound of formula II



II

wherein

X is selected from NR1, O, S;

Y1 and **Y2** are independently selected from O, S;

Z is selected from O, S, SO, SO_2, $SO_2N(R6)$, $N(R7)SO_2$, $N(R7)SO_2N(R6)$;

m is 1 or 2;

A is selected from a direct bond, (C1-6)alkyl, (C1-6)haloalkyl, or (C1-6)heteroalkyl containing a hetero group selected from N, O, S, SO, SO2 or containing two hetero groups selected from N, O, S, SO, SO2 and separated by at least two carbon atoms;

R1 is selected from H, (C1-3)alkyl, haloalkyl;

Each **R2** and **R3** is independently selected from H, halogen (preferably fluorine), alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkylaryl, alkyl-heteroaryl, heteroalkyl-aryl, heteroalkyl-heteroaryl, aryl-alkyl, aryl-heteroalkyl, heteroaryl-alkyl, heteroaryl-heteroalkyl, aryl-aryl, aryl-heteroaryl, heteroaryl-aryl, heteroaryl-heteroaryl, cycloalkyl-alkyl, heterocycloalkyl-alkyl, alkyl-cycloalkyl, alkyl-heterocycloalkyl;

Each **R4** is independently selected from H, halogen (preferably fluorine), (C1-3)alkyl or haloalkyl;

R6 is selected from H, alkyl, heteroalkyl, heterocycloalkyl, aryl, heteroaryl, alkylaryl, alkyl-heteroaryl, heteroalkyl-aryl, heteroalkyl-heteroaryl, arylalkyl, aryl-heteroalkyl, heteroaryl-alkyl, heteroaryl-heteroalkyl, aryl-aryl, aryl-heteroaryl, heteroaryl-aryl, heteroaryl-heteroaryl;

Each of the **R2, R3** and **R6** radicals may be independently optionally substituted with one or more (preferably one) groups selected from alkyl, heteroalkyl, aryl, heteroaryl, halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, thiol, alkylthiol, arylthiol, alkylsulfon, haloalkylsulfon, arylsulfon, aminosulfon, N-alkylaminosulfon, N,N-dialkylaminosulfon, arylaminosulfon, amino, N-alkylamino, N,N-dialkylamino, amido, N-alkylamido, N,N-dialkylamido, cyano, sulfonamino, alkylsulfonamino, arylsulfonamino, amidino, N-aminosulfon-amidino, guanidino, N-cyano-guanidino, thioguanidino, 2-nitro-ethene-1,1-diamin, carboxy, alkyl-carboxy, nitro, carbamate;

Optionally **R2** and **R3** may join to form a ring comprising up to 7 ring atoms, or R2 and R4 may join to form a ring comprising up to 7 ring atoms, or R2 and R6 may join to form a ring comprising up to 7 ring atoms, or R3 and R4 may join to form a ring comprising up to 7 ring atoms, or R3 and R6 may join to form a ring comprising up to 7 ring atoms, or R4 and R6 may join to form a ring comprising up to 7 ring atoms;

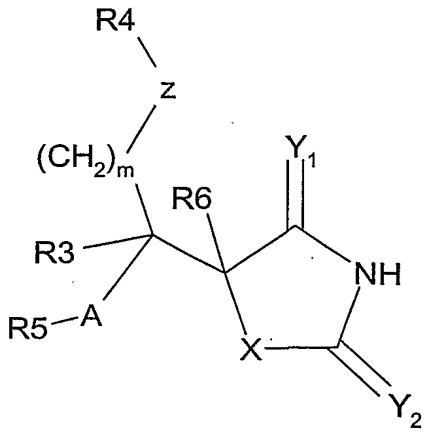
R5 is a monocyclic, bicyclic or tricyclic group comprising one, two or three ring structures each of up to 7 ring atoms independently selected from cycloalkyl, aryl, heterocycloalkyl or heteroaryl, with each ring structure being independently optionally

substituted by one or more substituents independently selected from halogen, hydroxy, alkyl, alkoxy, haloalkoxy, amino, N-alkylamino, N,N-dialkylamino, alkylsulfonamino, alkylcarboxyamino, cyano, nitro, thiol, alkylthiol, alkylsulfonyl, haloalkylsulfonyl, alkylaminosulfonyl, carboxylate, alkylcarboxylate, aminocarboxy, N-alkylamino-carboxy, N,N-dialkylamino-carboxy, wherein any alkyl radical within any substituent may itself be optionally substituted with one or more groups selected from halogen, hydroxy, alkoxy, haloalkoxy, amino, N-alkylamino, N,N-dialkylamino, N-alkylsulfonamino, N-alkylcarboxyamino, cyano, nitro, thiol, alkylthiol, alkylsulfonyl, N-alkylaminosulfonyl, carboxylate, alkylcarboxy, aminocarboxy, N-alkylaminocarboxy, N,N-dialkylaminocarboxy, carbamate;

when **R5** is a bicyclic or tricyclic group, each ring structure is joined to the next ring structure by a direct bond, by -O-, by (C1-6)alkyl, by (C1-6)haloalkyl, by (C1-6)heteroalkyl, by (C1-6)alkenyl, by (C1-6)alkynyl, by sulfone, by CO, by NCO, by CON, by NH, by S, by C(OH) or is fused to the next ring structure;

R7 is selected from (C1-6) alkyl, (C3-7)cycloalkyl, (C2-6)heteroalkyl, (C2-6)cycloheteroalkyl; or

(b) a compound of formula III



III

wherein

X is selected from NR1, O, S;

Y1 and **Y2** are independently selected from O, S;

Z is selected from NR2, O, S;

m is 0 or 1;

A is selected from a direct bond, (C1-6)alkyl, (C1-6) alkenyl, (C1-6)haloalkyl, or (C1-6)heteroalkyl containing a hetero group selected from N, O, S, SO, SO2 or containing two hetero groups selected from N, O, S, SO, SO2 and separated by at least two carbon atoms;

R1 is selected from H, alkyl, haloalkyl;

R2 is selected from H, alkyl, haloalkyl;

R3 and **R6** are independently selected from H, halogen (preferably F), alkyl, haloalkyl, alkoxyalkyl, heteroalkyl, cycloalkyl, aryl, alkyl-cycloalkyl, alkyl-heterocycloalkyl, heteroalkyl-cycloalkyl, heteroalkyl-heterocycloalkyl, cycloalkyl-alkyl, cycloalkyl-heteroalkyl, heterocycloalkyl-alkyl, heterocycloalkyl-heteroalkyl, alkylaryl, heteroalkyl-aryl, heteroaryl, alkylheteroaryl, heteroalkyl-heteroaryl, arylalkyl, aryl-heteroalkyl, heteroaryl-alkyl, heteroaryl-heteroalkyl, bisaryl, aryl-heteroaryl, heteroaryl-aryl, bisheteroaryl, cycloalkyl or heterocycloalkyl comprising 3 to 7 ring atoms, wherein the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl or heterocycloalkyl radicals may be optionally substituted by one or more groups independently selected from hydroxy, alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, hydroxyalkyl, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, carboxy, carboxyalkyl, alkylcarboxy, amino, N-alkylamino, N,N-dialkylamino, alkylamino, alkyl(N-alkyl)amino, alkyl(N,N-dialkyl)amino, amido, N-alkylamido, N,N-dialkylamido, alkylamido, alkyl(N-alkyl)amido, alkyl(N,N-dialkyl)amido, alkylcarbamate, alkylcarbamide, thiol, sulfone, sulfonamino, alkylsulfonamino, arylsulfonamino, sulfonamido, haloalkyl sulfone, alkylthio, arylthio, alkylsulfone, arylsulfone, aminosulfone, N-alkylaminosulfone, N,N-dialkylaminosulfone, alkylaminosulfone, arylaminosulfone, cyano, alkylcyano, guanidino, N-cyano-guanidino, thioguanidino, amidino, N-aminosulfon-amidino, nitro, alkylnitro, 2-nitro-ethene-1,1-diamine;

R4 is selected from H, alkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, haloalkoxy, aminoalkyl, amidoalkyl, thioalkyl;

R5 is a monocyclic, bicyclic or tricyclic group comprising one, two or three ring structures each of 3 to 7 ring atoms independently selected from cycloalkyl, aryl, heterocycloalkyl or heteroaryl, with each ring structure being independently optionally substituted by one or more substituents independently selected from halogen, thiolo, thioalkyl, hydroxy, alkylcarbonyl, haloalkoxy, amino, N-alkylamino, N,N-dialkylamino, cyano, nitro, alkyl, haloalkyl, alkoxy, alkyl sulfone, alkylsulfonamido, haloalkyl sulfone, alkylamido,alkylcarbamate, alkylcarbamide, carbonyl, carboxy, wherein any alkyl radical within any substituent may itself be optionally substituted by one or more groups independently selected from halogen, hydroxy, amino, N-alkylamino, N,N-dialkylamino, alkylsulfonamino, alkylcarboxyamino, cyano, nitro, thiol, alkylthiol, alkylsulfono, alkylaminosulfono, alkylcarboxylate, amido, N-alkylamido, N,N-dialkylamido, alkylcarbamate, alkylcarbamide, alkoxy, haloalkoxy, carbonyl, carboxy;

when **R5** is a bicyclic or tricyclic group, each ring structure is joined to the next ring structure by a direct bond, by -O-, by –S-, by-NH-, by (C1-6)alkyl, by (C1-6)haloalkyl, by (C1-6)heteroalkyl, by (C1-6)alkenyl, by (C1-6)alkynyl, by sulfone, by carboxy(C1-6)alkyl, or is fused to the next ring structure;

Optionally **R2** and **R4** may join to form a ring comprising up to 7 ring atoms or R3 and R6 may join to form a ring comprising up to 7 ring atoms.

7. A method of treating a metalloproteinase mediated disease or condition which comprises administering to a warm-blooded animal a therapeutically effective amount of a metalloproteinase inhibitor compound or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof wherein the metalloproteinase inhibitor compound is as claimed in any of claims 1 to 6.

8. Use of a metalloproteinase inhibitor compound or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof in the preparation of a medicament for use in the treatment of a disease or condition mediated by one or more metalloproteinase enzymes, wherein the metalloproteinase inhibitor compound is as claimed in any of claims 1 to 6.

9. A pharmaceutical composition for use in the treatment of a disease or condition mediated by one or more metalloproteinase enzymes which comprises a metalloproteinase inhibitor compound or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof and pharmaceutically acceptable carrier, wherein the metalloproteinase inhibitor compound is as claimed in any of claims 1 to 6.

10. A method of treating a metalloproteinase mediated disease or condition which comprises administering to a warm-blooded animal a therapeutically effective amount of a pharmaceutical composition which comprises a metalloproteinase inhibitor compound or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof and pharmaceutically acceptable carrier, wherein the metalloproteinase inhibitor compound is as claimed in any of claims 1 to 6.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/00475

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 233/78, C07D 401/12, C07D 403/12, C07D 405/12, A61K 31/4166, A61K 31/454, A61K 31/4439, A61P 35/00, A61P 11/00, A61P 19/00, A61P 29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, CHEM.ABS.DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts, Volume 65, 1966, ABSTRACT No. 13684 h, M. Lora-Tamayo et al: "Potential anti-cancer agents. I. Glutamine sulfonate analogs", Anales Real Soc. Espan. Fis. Quim. (Madrid), Ser.B. 62(2), 173-86 --	1-10
X	STN International, File CAPLUS, CAPLUS accession number 1968:506154, Document number 69:106154, Lora-Tamayo M. et al: "Potential anticancer agents. VI. Sulfonic analogs of aspartic acid", An.Quim. (1968), 64(6), 591-606 --	1-10

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 July 2002	15 -07- 2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer EVA JOHANSSON/BS Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/00475

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File CAPLUS, CAPLUS accession number 1974:463633, Document number 81:63633, Blaha, Ludvik et al: "5-Methyl-5-phenoxymethyl-hydantoins", & CS151744,B,19731119	1-10
X	US 3529019 A (JOHN T. SUH, MEQUOUN ET AL), 15 Sept 1970 (15.09.70)	1-10
X	US 3849574 A (JOHN T. SUH, MEQUOUNET AL), 19 November 1974 (19.11.74)	1-10
A	EP 0640594 A1 (FUJIREBIO INC.), 1 March 1995 (01.03.95)	1-10
A	WO 9906361 A2 (ABBOTT LABORATORIES), 11 February 1999 (11.02.99)	1-10
A	WO 9924399 A1 (DARWIN DISCOVERY LIMTED), 20 May 1999 (20.05.99)	1-10
A	WO 0040577 A1 (AVENTIS PHARMACEUTICALS INC.), 13 July 2000 (13.07.00)	1-10
A	WO 0105756 A1 (PHARMACIA & UPJOHN SPA), 25 January 2001 (25.01.01)	1-10
A	WO 0075106 A2 (WISCONSIN ALUMNI RESEARCH FOUNDATION), 14 December 2000 (14.12.00)	1-10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/00475

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 7 and 10
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet*

2. ☒ Claims Nos.: 1-10
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see next sheet**

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

*
Claims 1-10 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

**
Present claims 1-10 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the claims, which appear to be supported, and disclosed, namely those parts related to the compounds according to the examples in the description.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/00475

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3529019 A	15/09/70	NONE	
US 3849574 A	19/11/74	NONE	
EP 0640594 A1	01/03/95	JP 7126258 A	16/05/95
WO 9906361 A2	11/02/99	AU 8513998 A	22/02/99
		BG 103995 A	31/07/00
		BR 9810760 A	27/11/01
		CN 1261876 T	02/08/00
		EP 1001930 A	24/05/00
		HU 0002037 A	28/05/01
		JP 2001523272 T	20/11/01
		NO 996579 A	24/01/00
		NZ 501166 A	21/12/01
		PL 337854 A	11/09/00
		SK 170599 A	16/05/00
		TR 9903287 T	00/00/00
		ZA 9806828 A	29/01/99
WO 9924399 A1	20/05/99	AU 1046999 A	31/05/99
		BR 9814147 A	03/10/00
		CA 2308359 A	20/05/99
		CN 1283183 T	07/02/01
		EP 1030836 A	30/08/00
		GB 9723906 D	00/00/00
		JP 2001522832 T	20/11/01
		NO 20002440 A	11/05/00
		PL 340551 A	12/02/01
		US 6187924 B	13/02/01
		ZA 9810360 A	12/11/99
		GB 9802618 D	00/00/00
		GB 9813933 D	00/00/00
WO 0040577 A1	13/07/00	AU 1817700 A	24/07/00
		EP 1150975 A	07/11/01
WO 0105756 A1	25/01/01	AU 6689900 A	05/02/01
		EP 1200398 A	02/05/02
		GB 9916562 D	00/00/00
WO 0075106 A2	14/12/00	AU 3929600 A	28/12/00
		US 6294694 B	25/09/01
		US 2002032347 A	14/03/02